IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
Malcolm J. Simons	)	Examiner: Sisson, Bradley L.
	)	
Application No: 09/935,998	)	Art Unit: 1634
	)	
Filed: August 23, 2001	)	
	)	
For: Intron Sequence Analysis Method for Detection of Adjacent and Remote Locus Alleles as Haplotypes	)	

AMENDED APPEAL BRIEF IN SUPPORT OF APPELLANT'S APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES

Sir/Madame:

Applicant Genetic Technologies Limited (hereafter "Appellant") hereby submits this Amended Brief in support of its appeal from a decision by the Examiner, mailed March 31, 2004, in the above-referenced application, and in response to a request for Amended Appeal Brief mailed January 25, 2005. Appellant respectfully requests consideration of this Appeal by the Board of Patent Appeals and Interferences (the "Board") for allowance of the above-captioned patent application.

On June 30, 2004, Appellant filed a Notice of Appeal for the present application. The claims of the present application were finally rejected by the Examiner in a final Office Action mailed March 31, 2004 (the "**Final Action**"). An initial Appeal Brief was filed on September 30, 2004. The deadline for filing an Amended Appeal Brief was February 25, 2005. A petition for a five-month extension of time, with appropriate extension fee under 37 C.F.R. 1.191 and 37 C.F.R. 1.136, accompanies this Brief. If any additional fees are due, the Commissioner is authorized to charge Deposit Account No. 06-0029. Therefore, this is a proper Appeal and Appellant's Brief in support of this Appeal follows.

REAL PARTY IN INTEREST

The real party in interest in this Appeal is Genetic Technologies Limited of 60-66 Hanover Street, Fitzroy, Victoria 3065, Australia, the assignee of a 100% interest in U.S. Patent Application Serial No. 09/935,998, by virtue of an assignment from GeneType AG to Genetic Technologies Limited executed on November 7, 2002, and recorded at reel/frame 013577/0720. GeneType AG had previously been assigned a 100% interest in USSN 09/935,998 by virtue of an assignment in the grandparent application USSN 07/551,239, of which USSN 09/935,998 is a continuation, from the sole inventor, Dr. Malcolm J. Simons, to GeneType AG recorded at reel/frame 005423/0553.

RELATED APPEALS AND INTERFERENCES

There are no known appeals or interferences related to this Appeal. There is a related judicial proceeding in the U.S. District Court for the Northern District of California, No. C 03-1316 PJH, Judge Phyllis J. Hamilton presiding, concerning U.S. Patent No. 5,612,179 (hereafter "the '179 patent"), of which the instant application is a continuation, along with U.S. Patent No. 5,851,762, which is not directly related to the instant application. A Markman hearing was held and a court order concerning claim construction was rendered. A copy of the Court's Markman order, amended Markman order and the Parties' Amended Joint Claim Construction Statement are attached (Appendix B).

STATUS OF CLAIMS

Claims 1-3, 5-9, 11-15, 17-21, 23 and 25-30 are currently pending in the above-referenced application. The Final Office Action rejected all pending claims under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement. The Final Office Action also rejected all pending claims under 35 U.S.C. § 112, first paragraph as failing to comply with the enablement requirement. The Final Office Action rejected all pending claims under 35 U.S.C. § 112, second paragraph as being indefinite. The Final Office Action also rejected all pending claims under 35 U.S.C. § 103 as obvious over U.S. Patent No. 4,582,788 to Erlich (hereafter "Erlich") in view of EP 0256630 to Woo et al. (hereafter "Woo et al.")

Claims 1-3, 5-9, 11-15, 17-21, 23 and 25-30 as set forth in the Amendment, dated October 1, 2003, are the subject of this Appeal. Appendix A below sets forth a copy of the appealed claims.

STATUS OF AMENDMENTS

An amendment after final office action was submitted on June 30, 2004. An Advisory Action mailed on July 16, 2004 declined to enter the proposed amendment. A copy of all claims on appeal is attached hereto in Appendix A.

SUMMARY OF CLAIMED SUBJECT MATTER

The above-captioned patent application generally relates to the use of amplified non-coding sequence variants to determine at least one haplotype encompassing a human leukocyte antigen (HLA) locus. (Spec. at page and line numbers 6:16-32; 7:9-11) The application is based on the discovery that non-coding regions of genomic DNA are informative for determining haplotypes of loci that are in genetic linkage with the non-coding regions. (Spec. at 6:16-32)

For convenience, the text of the pending independent claims is reproduced below. A summary and discussion of support for the elements of each independent claim follows each such claim.

Claim 1. (previously presented) A method of determining at least one haplotype encompassing a human HLA genetic coding locus comprising:

(a) amplifying human genomic DNA, wherein the amplified genomic DNA comprises a non-coding region sequence that is in genetic linkage with an HLA genetic coding locus;

(b) detecting one or more sequence variations in the non-coding region; and

(c) using the one or more non-coding region sequence variations to determine at least one haplotype encompassing the human HLA genetic coding locus.

The subject matter of claim 1 concerns amplifying genomic human DNA comprising a non-coding region sequence that is in genetic linkage with an HLA locus and using one or more sequence variations in the non-coding region to determine at least one haplotype encompassing the HLA locus. [e.g., Specification at pages and line numbers 6:16 to 7:3; 7:16 to 8:34; 98:1-12]

Support for each element of claim 1 follows. While Appellant's position is that the claim preamble is not a limitation on the scope of claim 1, for completeness a discussion of support for the claim preamble is included.

The preamble recites, "determining at least one haplotype." Support for the individual terms and the phrase as a whole may be found in the Specification at least at page and line numbers 1:11; 6:16-19; 6:36 to 7:11; 7:16-24; 8:14-26; 9:22-28; 13:3-18; 13:33 to 14:2; 21:4-24; 74:1 to 77:4; 98:1-2; Example 3 and numerous other locations.

The preamble further recites, "encompassing a human HLA genetic coding locus." Support for the individual terms and the phrase as a whole may be found in the Specification at least at page and line numbers 2:24-25; 7:9-11; 9:36 to 10:4; 11:3-9; 12:11-13; 14:3-20; 15:18-22; 16:16-19; 21:19-23; 31:16-20; 33:22-32; 42:10 to 44:13; 65:14 to 70:1; 75:19-22; and Examples 1-5.

Element (a) of claim 1 recites, "amplifying human genomic DNA, wherein the amplified genomic DNA comprises a non-coding region sequence that is in genetic linkage with an HLA genetic coding locus." Support for the individual terms and the phrase as a whole may be found at least at page and line numbers 2:24-25; 6:19-22; 7:9-31; 8:14-26; 9:8-13; 9:29 to 10:4; 11:3-9; 12:11-13; 16:5 to 18:27; 24:1 to 30:35; 42:10 to 65:10; 98:1-4 and Examples 1-5.

Element (b) of claim 1 recites, "detecting one or more sequence variations in the non-coding region." Support for the individual terms and the phrase as a whole may be found in the Specification at least at page and line numbers 6:26 to 7:11; 7:28 to 8:34; 9:29 to 10:4; 18:28 to 21:24; 31:1 to 40:31; 98:6-11 and Examples 1-5.

Element (c) of claim 1 recites, "using the one or more non-coding region sequence variations to determine at least one haplotype encompassing the human HLA genetic coding locus." Support for the individual terms and the phrase as a whole may be found in the Specification at least at page and line numbers 2:24-25; 6:16 to 7:11; 7:16 to 8:34; 9:22 to 10:4; 11:3-21; 12:11-13; 15:16-26; 16:4 to 21:23; 42:10 to 70:1; 75:19 to 76:2; 98:1-11 and Examples 1-5.

Claim 13. (previously presented) A method for determining at least one haplotype encompassing a multi-allelic human HLA genetic coding locus comprising:

(a) amplifying human genomic DNA with a primer pair that spans a non-coding region sequence, said primer pair defining a DNA sequence which is in genetic linkage with said HLA genetic coding locus and contains a sufficient number of non-coding region sequence nucleotides to produce an amplified DNA sequence characteristic of said at least one haplotype;

(b) analyzing the amplified DNA sequence to detect one or more sequence variations in the non-coding region; and

(c) using the one or more non-coding region sequence variations to determine at least one haplotype encompassing the multiallelic human HLA genetic coding locus.

The subject matter of claim 13 concerns using a primer pair that spans a non-coding region sequence to amplify genomic human DNA. The amplified sequence is in genetic linkage with a multi-allelic HLA locus. The non-coding region sequence contains one or more sequence variations that are characteristic of at least one haplotype of the HLA locus. The amplified DNA sequence is analyzed to detect the one or more sequence variations, which are used to determine at least one haplotype of the HLA locus. [E.g., Specification at page and line numbers 1:11-12; 6:16 to 7:3; 7:9-11; 7:16 to 8:34; 98:1-12] Support for each element of claim 13 follows.

Although Appellant asserts that the preamble is not a limitation on the scope of claim 13, for completeness a discussion of support for the claim preamble is included. The preamble of claim 13 differs from the preamble of claim 1 in its use of the term "multi-allelic." Support for that term may be found in the Specification at least at page and line numbers 9:5-7; 12:16-21; 12:31 to 13:5; 13:21 to 15:15; 20:15-19; 34:23-27; 42:11 to 44:13; 74:1 to 78:9 and Examples 1-8. Support for the remaining terms and the phrase as a whole is as recited above for the preamble to claim 1, and includes at least page and line numbers 1:11; 2:24-25; 6:16-19; 6:36 to 7:11; 7:16-24; 8:14-26; 9:22-28; 9:36 to 10:4; 11:3-9; 12:11-13; 13:3-18; 13:33 to 14:20; 15:18-22; 16:16-19; 21:4-24; 31:16-20; 33:22-32; 42:10 to 44:13; 65:14 to 70:1; 74:1 to 77:4; 98:1-2; and Examples 1-5.

Element (a) of claim 13 recites, "amplifying human genomic DNA with a primer pair that spans a non-coding region sequence, said primer pair defining a DNA sequence which is in genetic linkage with said HLA genetic coding locus and contains a sufficient number of non-coding region sequence nucleotides to produce an amplified DNA sequence characteristic of said

at least one haplotype." Support for the individual terms and for the phrase as a whole may be found in the Specification at least at page and line numbers 1:11-12; 2:22-33; 6:16 to 7:3; 7:9-11; 7:16 to 8:34; 9:8-13; 9:22 to 10:13; 10:19-24; 10:31 to 11:21; 12:11 to 18:27; 21:4 to 30:35; 42:10 to 65:12; 98:1-12 and Examples 1-5.

Element (b) of claim 13 recites, "analyzing the amplified DNA sequence to detect one or more sequence variations in the non-coding region." Support for the individual terms and for the phrase as a whole may be found in the Specification at least at page and line numbers 6:24 to 7:3; 7:16-18; 7:35 to 8:34; 9:29 to 10:13; 16:5-25; 18:28 to 21:24; 31:1 to 40:31; 42:10 to 56:30; 65:14 to 78:9 and Examples 1-8.

Element (c) of claim 13 recites, "using the one or more non-coding region sequence variations to determine at least one haplotype encompassing the multiallelic human HLA genetic coding locus." Support for the individual terms and for the phrase as a whole may be found in the Specification at least at page and line numbers 1:11-12; 2:22-33; 6:16 to 7:3; 7:16 to 8:34; 9:5-7; 9:22 to 10:8; 11:3-21; 12:11-21; 12:31 to 13:5; 13:21 to 21:23; 34:23-27; 42:10 to 56:30; 74:1 to 78:9; 98:1-11 and Examples 1-5.

Claim 19. (previously presented) A method for determining at least one haplotype encompassing a human HLA coding locus comprising:

(a) amplifying human genomic DNA with a primer pair that spans a non-coding region sequence, said primer pair defining a DNA sequence which is in genetic linkage with said HLA coding locus;

(b) analyzing the amplified DNA sequence to detect one or more sequence variations in the non-coding region; and

(c) using the one or more non-coding region sequence variations to determine at least one haplotype encompassing the human HLA coding locus.

The subject matter of claim 19 concerns using a primer pair that spans a non-coding region sequence to amplify genomic human DNA. The amplified sequence is in genetic linkage with an HLA locus and contains one or more sequence variations. The sequence variations in the non-coding region are used to determine at least one haplotype of the HLA locus. [e.g.,

Specification at pages and line numbers 1:11-12; 6:16 to 7:3; 7:9-11; 7:16 to 8:34; 98:1-12] Support for each element of claim 19 follows.

While Appellant's position is that the claim preamble is not a limitation on the scope of claim 19, for completeness a discussion of support for the claim preamble is included. The preamble of claim 19 is almost identical to the preamble of claim 1. Support for the individual terms and the phrase as a whole may be found in the Specification at least at page and line numbers 1:11; 2:24-25; 6:16-19; 6:36 to 7:11; 7:16-27; 8:14-26; 9:22-28; 9:36 to 10:4; 11:3-9; 12:11-13; 13:3-18; 13:33 to 14:20; 15:18-22; 16:16-19; 21:4-24; 31:16-20; 33:22-32; 42:10 to 44:13; 65:14 to 70:1; 74:1 to 77:4; 98:1-2; and Examples 1-5.

Element (a) of claim 19 recites, "amplifying human genomic DNA with a primer pair that spans a non-coding region sequence, said primer pair defining a DNA sequence which is in genetic linkage with said HLA coding locus." Support for the individual terms and for the phrase as a whole may be found in the Specification at least at page and line numbers 1:11-12; 2:22-25; 6:16-22; 7:9-11; 7:16-31; 9:8-21; 10:31 to 11:21; 12:11 to 18:27; 21:4 to 30:35; 42:10 to 65:12; 98:1-12 and Examples 1-5.

Element (b) of claim 19 recites, "analyzing the amplified DNA sequence to detect one or more sequence variations in the non-coding region," which is the same as element (b) of claim13. Support for the individual terms and for the phrase as a whole may be found in the Specification at least at page and line numbers 6:24 to 7:3; 7:16-27; 7:35 to 8:34; 9:29 to 10:13; 16:5-25; 18:28 to 21:24; 31:1 to 40:31; 42:10 to 56:30; 65:14 to 78:9 and Examples 1-8.

Element (c) of claim 19 recites, "using the one or more non-coding region sequence variations to determine at least one haplotype encompassing the human HLA coding locus." This language is almost identical to element (c) of claim 13. Support for the individual terms and for the phrase as a whole may be found in the Specification at least at page and line numbers 1:11-12; 2:22-33; 6:16 to 7:11; 7:16 to 8:34; 9:22 to 10:8; 11:3-21; 12:11-21; 12:31 to 21:23; 42:10 to 56:30; 74:1 to 78:9; 98:1-11 and Examples 1-5.

Appellant submits that there are no means plus function or step plus function claims pending.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The sub-headings below correspond to the sections of the Argument addressing each ground of rejection.

A. Claims 1-3, 5-9, 11-15, 17-21, 23 and 25-30 stand rejected as failing to comply with the written description requirement under 35 U.S.C. § 112, first paragraph.

B. Claims 1-3, 5-9, 11-15, 17-21, 23 and 25-30 stand rejected as failing to comply with the enablement requirement under 35 U.S.C. § 112, first paragraph.

C. Claims 1-3, 5-9, 11-15, 17-21, 23 and 25-30 stand rejected as indefinite under 35 U.S.C. § 112, second paragraph.

D. Claims 1-3, 5-9, 11-15, 17-21, 23 and 25-30 stand rejected as obvious under 35 U.S.C. § 103 over U.S. Patent No. 4,582,788 to Erlich ("Erlich") in view of EP 0256630 to Woo et al. ("Woo et al.")

ARGUMENT

A. The Rejection of the Claims under 35 U.S.C. § 112, 1st Paragraph as Failing to Comply with the Written Description Requirement is Based on an Improper Construction of Claim Scope.

The Final Office Action rejected the pending claims under 35 U.S.C. § 112, 1st paragraph as failing to comply with the written description requirement. As discussed in the Response to Final Action filed by facsimile on June 30, 2004, Applicant asserts that the above rejection under 35 U.S.C. § 112, 1st paragraph is based on a faulty construction of the claim scope.

Claim construction analysis begins with the words of the claims. [*See Vitronics Corp. v. Conceptrionic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)] "In construing claims, the analytical focus must begin and remain centered on the language of the claims themselves." [*Nystrom v. Trex Company, Inc.*, No. 031092v2 – 06/28/04 (Fed. Cir. 2004), citing *Ferguson Beauregard v. Mega Sys., Inc.*, 350 F.3d 1327, 1338 (Fed. Cir. 2003)] "In the absence of an express intent to impart a novel meaning to claim terms, an inventor's claim terms take on their ordinary meaning . . . . [T]he ordinary meaning must be determined from the standpoint of a person of ordinary skill in the relevant art." [*Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1325 (Fed. Cir. 2002)] During patent examination, pending claims are given their broadest reasonable

interpretation consistent with the specification. [*In re Hyatt*, 211 F.3d, 1367, 1372 (Fed. Cir. 2000)] However, the broadest reasonable interpretation of the claims must also be consistent with the interpretation that those skilled in the art would reach. [*In re Cortright,* 165 F.3d 1353, 1359 (Fed. Cir. 1999)]

1. The Claim Interpretation Encompassing Amplification of Entire Chromosome 6 is Unreasonable

The Final Action stated that, "For the purposes of examination, the phrase 'genetic linkage' has been interpreted as encompassing the entire chromosome upon which the HLA complex is found (chromosome 6). Accordingly, claims 1, 13, and 19 have been interpreted as encompassing amplification of entire chromosome 6." [Final Action at ¶ 10] The Final Action stated that the specification fails to disclose an adequate written description of the claimed methods, "where amplicons of any length are to be generated." [Final Action at ¶ 14] Appellant respectfully asserts that one of skill in the art would not have considered the interpretation encompassing the amplification of the entire chromosome 6 to be reasonable, in light of the claim language and specification.

It was well known in the art as of the date of the present application that chromosomes are millions of basepairs in length. In fact, chromosome 6, on which the HLA loci are found, is over 170,000,000 basepairs in length (see, *e.g.,* NCBI Map Viewer, *Homo sapiens*, Chromosome 6, www.ncbi.nlm.nih/gov/mapview/). Given the size of the entire chromosome 6, no skilled artisan would have considered it reasonable to interpret the claims to require amplification of the entire 170,000,000 basepair sequence.

That interpretation is unsupported by the claim language and the specification. For example, the text of Claim 1 of the pending application is cited below:

Claim 1. A method of determining at least one haplotype encompassing a human HLA genetic coding locus comprising:

(a) amplifying human genomic DNA, wherein the amplified genomic DNA comprises a non-coding region sequence that is in genetic linkage with an HLA genetic coding locus;

(b) detecting one or more sequence variations in the non-coding region; and

(c) using the one or more non-coding region sequence variations to determine at least one haplotype encompassing the human HLA genetic coding locus.

The Final Action focuses on the use of the term "genetic linkage" and asserts that the entire chromosome 6 may be in genetic linkage with the HLA loci. However, the Final Action completely ignores the first part of element (a), which recites, "amplifying human genomic DNA, wherein the amplified genomic DNA comprises a non-coding region sequence...." The phrase "amplifying human genomic DNA" requires that the sequence to be amplified must be amplifiable. This is further emphasized by reference to an "amplified genomic DNA" that results. Since a 170 million basepair (Mbp) sequence is not amplifiable, there could be no amplified genomic DNA encompassing all of chromosome 6.

As noted in previous Office Actions, the specification contains numerous references to amplified sequences, that are nowhere near 170 Mbp in size. For example: pg. 14, lines 9-11, ("Exon-limited primers can be used to produce an amplified sequence that includes as few as about 200 nucleotides..."); pg. 14, lines 31-32 ("About 300 to 500 nucleotides is sufficient..."); pg. 15, lines 11-14 ("The amplified sequences used to characterize highly polymorphic loci are generally between about 800 to about 2,0000 nucleotides..."); pg. 17, lines 28-29 ("Since PCR methodology can be used to amplify sequences of several Kb"). The specification discloses at pages 57 to 64 a number of exemplary primer pairs for amplification of various HLA loci sequences. Those generally would result in amplified sequences from slightly over one hundred to less than two thousand basepairs in length, although an amplified sequence as short as 53 basepairs in size is disclosed in the Examples (pg. 89, lines 27-29, shortest amplicon disclosed equals 207 minus 154, *i.e.,* 53 nucleotides).

Nowhere does the specification disclose an amplified DNA sequence even approaching 170 Mbp in size. Rather, the specification consistently recites amplified sequences ranging from about 50 to about 2,000 basepairs in size. Given the disclosure in the specification and the knowledge in the art, Appellant reiterates that no skilled artisan could reasonably interpret the scope of the claims to encompass "amplification of entire chromosome 6".

The Final Action's interpretation of claim scope is also inconsistent with other claim language. Claim 1 recites that one or more non-coding region sequence variations are detected

"to determine at least one haplotype encompassing the HLA locus." The specification defines "haplotype" at pg. 9, lines 22-28 as:

> ...a region of genomic DNA on a chromosome which is bounded by recombination sites such that genetic loci within a haplotypic region are usually inherited as a unit. However, occasionally, genetic rearrangements may occur within a haplotype. Thus, the term haplotype is an operational term that refers to the occurrence on a chromosome of linked loci.

It is clear that haplotypes occur on regions of chromosomal DNA that are bounded by recombination sites. Thus, the non-coding sequence variations that are of use to determine haplotypes are those that occur within the same haplotypic region as the haplotype to be determined. As such haplotypic regions do not extend over the entire chromosome 6, it is unreasonable to construe the scope of the claimed subject matter to "encompass amplification of entire chromosome 6."

As the rejection of the pending claims for failure to comply with the written description requirement is based upon an unreasonable construction of the claims, Appellant asserts that the rejection is improper. Given the disclosure of numerous exemplary embodiments in the specification of amplified sequences of a range of amplifiable sizes, Appellant asserts that the instant application provides ample written description support commensurate with the properly construed scope of the claims.

2. *The Interpretation Encompassing the Simultaneous Amplification and Analysis of at Least 50 Different Loci is Unreasonable*

The Final Action states that, "The claims have been interpreted as encompassing the amplification of all the loci, known and unknown, in a simultaneous manner, and wherein the amplicons for each of the loci is of like size and is similarly labeled as with any other amplicon for different loci." The Final Action further refers to the disclosure in the specification that the HLA complex comprises "'at least 50 loci.' Accordingly, the claimed method is considered to fairly encompass the simultaneous amplification and analysis of at least 50 different loci." [Final Action at ¶ 11]

Appellant reiterates that the Final Action's interpretation of claim scope is not reasonable. Nowhere does the claim language or specification support an interpretation that the claims cover the simultaneous amplification and analysis of at least 50 different loci. Claim 1

recites, "amplifying human genomic DNA, wherein the amplified genomic DNA comprises a non-coding region sequence that is in genetic linkage with an HLA genetic coding locus; detecting one or more sequence variations in the non-coding region; and using the one or more non-coding region sequence variations to determine at least one haplotype encompassing the human HLA genetic coding locus." On its face, the language refers to "an HLA genetic coding locus" and determining "at least one haplotype encompassing the HLA genetic coding locus," not to simultaneously amplifying and analyzing at least 50 different loci.

In support of its interpretation, the Final Action cites the language of claims 3, 15 and 21 to "two or more haplotypes are determined." Claim 1(c) recites, "using the one or more non-coding region sequence variations to determine at least one haplotype encompassing the HLA locus." It is clear from that language that the at least one (i.e. one or more) haplotypes encompass the HLA locus. This language reflects the possibility that a given HLA locus may exhibit multiple haplotypes in a population. The specification at pg. 2, lines 29-33 discloses that the majority of HLA loci were known to be polymorphic and would therefore exhibit multiple haplotypes within a population. At a minimum, chromosomal DNA from a given individual may exhibit two different haplotypes at a given HLA locus, as there would be two copies of each HLA gene present – one inherited from the mother and one from the father. Unless both parental chromosomes have identical haplotypes, a given HLA locus in DNA obtained from one individual would exhibit two different haplotypes.

The specification further discloses that the amplification, detection of non-coding sequence variations and determination of haplotype(s) may not result in the determination of a unique haplotype. Rather, analysis of HLA loci haplotypes may be of use where the haplotype(s) may be determined to belong to one of a group of possible haplotypes.

For example, the specification at pg. 74, lines 2-7 states that:

> Carriers of genetic diseases and those affected by the disease can be identified by use of the present method. Depending on the disease, the screening analysis can be used to detect the presence of one or more alleles associated with the disease or the presence of **haplotypes** associated with the disease. (emphasis added)

That is, the claimed methods are not limited to the determination of a unique haplotype encompassing an HLA locus, but rather may result in the determination of multiple haplotypes, such as those associated with a disease.

The specification discusses the cystic fibrosis (CF) locus as an example of a disease-associated locus. The specification at pg. 74:31 to 75:22 states that:

> Studies of haplotypes of parents of CF patients (who necessarily have one normal and one disease-associated haplotype) indicated that there are at least 178 haplotypes associated with the CF locus. Of those haplotypes, 90 are associated only with the disease; 78 are found only in normals; and 10 are associated with both the disease and with normals (Kerem et al, supra). The disease apparently is caused by several different mutations, some in very low frequency in the population. As demonstrated by the haplotype information, there are more haplotypes associated with the locus than there are mutant alleles responsible for the disease.
>
> A genetic screening program (based on amplification of exon regions and analysis of the resultant amplified DNA sequence with probes specific for each of the mutations or with enzymes producing RFLP patterns characteristic of each mutation) may take years to develop. Such tests would depend on detection and characterization of each of the mutations, or at least of mutations causing about 90 to 95% or more of the cases of the disease. The alternative is to detect only 70 to 80% of the CF-associated genes. That alternative is generally considered unacceptable and is the cause of much concern in the scientific community.
>
> The present method directly determines haplotypes associated with the locus and can detect haplotypes among the 178 currently recognized haplotypes associated with the disease locus.

The skilled artisan, reading the claims in light of the specification, would conclude that the phrase, "to determine at least one haplotype encompassing the HLA locus" refers to determining one or more possible haplotypes encompassing an HLA locus, not to "the amplification of all the loci, known and unknown, in a simultaneous manner, and wherein the amplicons for each of the loci is of like size and is similarly labeled as with any other amplicon for different loci" or to "the simultaneous amplification and analysis of at least 50 different loci" as asserted by the Final Action.

As discussed above, because the §112 written description rejection is based on an unreasonable interpretation of claim scope, Appellant asserts that the rejection is improper. The specification discloses the amplification, analysis and determination of haplotypes for numerous exemplary HLA loci, commensurate with the properly construed scope of the claims. Appellant thus asserts that there is ample written description support in the specification for the pending claims.

3. The Final Action Fails to Establish a Prima Facie Case for Lack of Written Description of Primers of Any Length

There is a strong presumption that an adequate written description of a claimed invention is present in the specification as filed. [MPEP §2163.03, citing *In re Wertheim*, 541 F.2d 257, 262 (CCPA 1976)] In order to support a *prima facie* case of lack of written description, the Examiner bears the initial burden of presenting, by a preponderance of the evidence, reasons why a person skilled in the art would not recognize a description of the invention defined by the claims. [MPEP §2163, citing *Wertheim*, 541 F.2d at 263] For the reasons discussed below, Appellant asserts that the Examiner has failed to establish a *prima facie* case of lack of written description.

The Final Action states that the claimed methods, "have also been interpreted as encompassing the use of any length and combination of primer..." [Final Action at ¶ 13] "A review of the specification fails to find an adequate description of the claimed methods wherein primers of any length are to be used..." [Final Action at ¶ 14] "Attention is also directed to page 22 of the disclosure where is taught that the primers used in the claimed methods are to range in size from 8 to 30 nucleotides. Accordingly, the specification does not reasonably support the position that [Appellant] contemplated, much less possessed, methods where primers of lengths outside of 8 to 30 nucleotides were to be used..." [*Id.*]

Appellant initially notes that page 22 of the specification does not appear to support the assertion that "[it] is taught that the primers used in the claimed methods are to range in size from 8 to 30 nucleotides." For convenience, the cited section of the specification is reproduced below.

> Each locus-specific primer includes a number of nucleotides which, under the conditions used in the hybridization, are sufficient to hybridize with an allele of the locus to be amplified and to be free from hybridization with alleles of other loci. The specificity of the primer increases with the number of nucleotides in its sequence under conditions that provide the same stringency. Therefore, longer primers are desirable. Sequences with fewer than 15 nucleotides are less certain to be specific for a particular locus. That is, sequences with fewer than 15 nucleotides are more likely to be present in a portion of the DNA associated with other genetic loci, particularly loci of other common origin or evolutionarily closely related origin, in inverse proportion to the length of the nucleotide sequence.

> Each primer preferably includes at least about 15 nucleotides, more preferably at least about 20 nucleotides. The primer preferably does not exceed about 30 nucleotides, more preferably about 25 nucleotides. Most preferably, the primers have between about 20 and about 25 nucleotides.
>
> A number of preferred primers are described herein. Each of those primers hybridizes with at least about 15 consecutive nucleotides of the designated region of the allele sequence. For many of the primers, the sequence is not identical for all of the other alleles of the locus. For each of the primers, additional preferred primers have sequences which correspond to the sequences of the homologous region of other alleles of the locus or to their complements.
>
> When two sets of primer pairs are used sequentially, with the second primer pair amplifying the product of the first primer pair, the primers can be the same size as those used for the first amplification. However, smaller primers can be used in the second amplification and provide the requisite specificity. These smaller primers can be selected to be allele-specific, if desired. The primers of the second primer pair can have 15 or fewer, preferably 8 to 12, more preferably 8 to 10 nucleotides. When two sets of primer pairs are used to produce two amplified sequences, the second amplified DNA sequence is used in the subsequent analysis of genetic variation and must meet the requirements discussed previously for the amplified DNA sequence.

It is clear from the text of the Specification that the Final Action's assertion, "that the primers used in the claimed methods are to range in size from 8 to 30 nucleotides" represents a preferred embodiment. Thus, "The primers of the second primer pair can have 15 or fewer, preferably 8 to 12, more preferably 8 to 10 nucleotides" Also, "The primer preferably does not exceed about 30 nucleotides..." There is no basis in the specification or the claim language to attempt to limit the claimed subject matter to the disclosed preferred embodiments.

The specification as cited above states that, "Each locus-specific primer includes a number of nucleotides which, under the conditions used in the hybridization, are sufficient to hybridize with an allele of the locus to be amplified and to be free from hybridization with alleles of other loci." There is no explicit size limit expressed concerning the primers of use in the claimed methods. The only stated requirement [for locus specific primers] is that the primers include a sufficient number of nucleotides to hybridize with the locus to be amplified and not to other loci.

As of the date of the instant application, it was well known in the art how to make and use primers. The specification provides guidance to the skilled artisan as to exemplary methods for primer preparation. For example, at pg. 23, lines 20-33:

> The primers can be prepared using a number of methods, such as, for example, the phosphotriester and phosphodiester methods or automated embodiments thereof. The phosphodiester and phosphotriester methods are described in Cruthers, Science 230:281-285 (1985); Brown et al, Meth. Enzymol., 68:109 (1979); and Nrang et al, Meth. Enzymol., 68:90 (1979). In one automated method, diethylphosphoramidites which can be synthesized as described by Beaucage et al, Tetrahedron letters, 22:1859-1962 (1981) are used as starting materials. A method for synthesizing primer oligonucleotide sequences on a modified solid support is described in U.S. Pat. No. 4,458,066.

The exemplary methods recited above are not limited to primers of between 8 and 30 nucleotides in length. Rather, using such methods, primers of a wide range of lengths may be prepared. The specification at pages 57-64, 83 and 89-93 discloses a large number of exemplary primers of different sizes.

The written description requirement does not require that the claimed subject matter be described *in haec verba* (i.e., using the same terms) in order to satisfy the written description requirement. [MPEP §2163.02] Appellant respectfully asserts that, given the ample disclosure in the specification of numerous exemplary embodiments within the scope of the claimed subject matter, the skilled artisan would recognize that the instant inventor had invented the claimed subject matter, without limitation as to the size of the primers used. [*See, e.g., In re Gosteli,* 872 F.2d 1008, 1012 (Fed. Cir. 1989)]

4. The Specification Contains Written Description Support for a Representative Number of Species of the Genus of HLA Loci

The Final Action at pg. 7, ¶ 14 states that, "While the specification does provide a description of analyzing the HLA DQA1 locus in humans, the specification has not been found to provide the requisite description of such a broad genus as claimed." The written description requirement for a genus claim may be satisfied through sufficient description of a representative number of species. [MPEP §2163, citing *Regents of the Univ. of California v. Eli Lilly & Co.*, 119F.3d 1559, 1568 (Fed. Cir. 1997)] A 'representative number of species' means that the species are representative of the entire genus. [MPEP §2163] Disclosure of a single species within a genus may provide adequate written description support for the genus. [*E.g., In re Herschler,* 591 F.2d 693, 697 (CCPA 1979)] "Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces." [MPEP §2163]

The Final Action at ¶16 acknowledges that the Specification provides primers for the HLA-A, HLA-B, HLA-C, DQA1, DRA, DRB, DQB1 and DPB1 loci. The Specification at pg. 2, lines 25-30 states that for the purpose of HLA tissue typing, two main classes of loci are recognized – the Class I loci (A, B and C) and the Class II loci (DRA, DRB, DQA1, DQB, DPA and DPB). U.S. Patent No. 4,582,788 (Erlich) states that, "The major histocompatibility complex (MHC) of humans is a cluster of genes occupying a region located on the sixth chromosome. This complex, denoted HLA (Human Leukocyte Antigen), has been divided into five major gene loci, which according to World Health Organization nomenclature are designated HLA-A, HLA-B, HLA-C, HLA-D and HLA-DR. The A, B, and C loci are single gene loci. The D and DR loci are multi-gene loci." According to U.S. Patent No. 6,194,147 (Baxter-Lowe *et al.*), "The major histocompatibility complex of humans (denoted HLA—human leukocyte antigen) is a cluster of genes occupying a region located on the sixth chromosome. The polymorphic proteins encoded by the HLA region have been designated HLA-A, -B, -C, -DR, -DQ, and -DP...D-region proteins are encoded by loci designated DRA, DRB1, DRB3, BRB4, DQA1, DQB1, DPA1, and DPB1."

Appellant respectfully asserts that the Specification discloses a representative number of species, including representatives of each of the major HLA gene loci known as of the priority date of the instant application, in satisfaction of the written description requirement for the genus of HLA loci.

5. The Specification Contains Written Description for Determining Haplotypes Encompassing HLA Loci

The Final Action at ¶ 17 asserts that, "the specification is essentially silent as to which mutations for any and all HLA loci are to be correlated, directly and indirectly, with any disease (claims 5 and 17)...the specification is silent as to how one is to identify useful mutations from useless mutations when the disease is multigenic in origin and the genes, much less the mutation involved in causing the disease, are not known" However, the claims do not require correlation of specific mutations with a disease state. To reiterate, Claim 1 concerns a method for determining at least one haplotype encompassing a human HLA genetic locus. It says nothing about determining specific mutations correlated with a disease. Claim 5 recites the method of Claim 1, wherein the haplotype is associated with a disease. Again, it says nothing about determining specific mutations correlated with the disease.

The Specification provides detailed instructions for how to determine haplotypes by several different analytical methods. It provides specific, non-limiting examples of haplotype determination, such as Examples 3 and 4 for the HLA-DQA1 locus. Methods for determining haplotypes associated with a disease are disclosed in the Specification at pages 74-78. The Specification explicitly states that, "neither the mutation site nor the location for a disease gene is required to determine haplotypes associated with the disease. Amplified intron sequences in the regions of closely flanking RFLP markers, such as are known for Huntington's disease and many other inherited diseases, can provide sufficient information to screen for haplotypes associated with the disease."

The Final Action's argument for lack of written description is based on an element that is not present in any of the claims. Adequate written description support is provided for the claimed subject matter of determining haplotypes encompassing HLA loci.

B. The Specification Satisfies the Enablement Requirement Under 35 U.S.C. § 112, 1st Paragraph.

The Final Action at ¶21 asserts that the claims lack enablement, "as one cannot enable that which they do not have possession of." As discussed above, the rejection for lack of written description support was based on an incorrect construction of the claims. Because there is adequate written description support for the properly construed scope of the claims, the enablement rejection based on lack of written description support is improper.

1. Amplification Methods Were Well Known in the Art and Fully Enabled by the Specification

Paragraph 22 of the Final Action refers to "amplification artifacts due to error on the part of the polymerase as well as because of mis-priming, including primer-dimer formation." That paragraph also refers to the claimed method encompassing "any number of amplification steps" and using "any level of stringency".

Various amplification techniques, such as PCR amplification, were well known in the art as of the priority date of the instant application. For example, U.S. Patent No. 4,683,195 (Mullis, attached as Appendix C), incorporated by reference into the instant application, provided a detailed description of the PCR process, including primer selection and synthesis and

hybridization conditions suitable for general use in PCR amplification. The Mullis reference covered the various factors cited in ¶22, such as incubation temperature, ionic strength, incubation time, denaturing reagents, base composition, *etc.*, all of which were well known in the art. U.S. Patent No. 4,683,194 (Saiki et al., attached as Appendix D), also incorporated by reference into the instant application, provided additional details on amplification and hybridization techniques.

Such general techniques were known to those of skill in the art. The skilled artisan was specifically directed to those and other references on amplification techniques at pages 24-30 of the Specification, which provided additional guidance to the artisan on various techniques, such as genomic DNA purification, hybridization conditions (*e.g.,* ionic strength, pH, temperature and time of incubation) and amplification methods. Particular non-limiting examples of conditions of use for amplification were disclosed in Examples 1-8. For instance, Example 1 recites:

> The extracted DNA from each sample is used to form two replicate aliquots per sample, each aliquot having 1 μg of sample DNA. Each replicate is combined in a total volume of 100 μl with a primer pair (1 μg of each primer), dNTPs (2.5 mM each) and 2.5 units of Taq polymerase in amplification buffer (50 mM KCl; 10 mM Tris-HCl, pH 8.0; 2.5 mM MgCl2; 100 μg/ml gelatin) to form four amplification reaction mixtures. The first primer pair contains the primers designated SGD005.IIVS1.LNP and SGD009.AIVS3.R2NP (A locus-specific). The second primer pair contains the primers designated SGD001.DQA1.LNP and SGD003.DQA1.RNP (DQA locus-specific). Each primer is synthesized using an Applied Biosystems model 308A DNA synthesizer. The amplification reaction mixtures are designated SA (suspect's DNA, A locus-specific primers), SD (suspect's DNA, DQA1 locus-specific primers), CA (crime scene DNA, A locus-specific primers) and CD (crime scene DNA, DQA1 locus-specific primers).
>
> Each amplification reaction mixture is heated to 94° C for 30 seconds. The primers are annealed to the sample DNA by cooling the reaction mixtures to 65° C for each of the A locus-specific amplification mixtures and to 55° C for each of the DQA1 locus-specific amplification mixtures and maintaining the respective temperatures for one minute. The primer extension step is performed by heating each of the amplification mixtures to 72° C for one minute. The denaturation, annealing and extension cycle is repeated 30 times for each amplification mixture.

That level of detail is more than sufficient to guide the skilled artisan in how to use the claimed methods. "As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied." [MPEP 2164.01(b), citing *In re*

Fisher, 427 F.2d 833, 839 (CCPA, 1970)] Given the ample guidance in the Specification and the extensive general knowledge in the art (*e.g.*, U.S. Patent No. 4,683,195), it would have been a matter of routine experimentation for the skilled artisan to select, design and implement primers and amplification conditions for any known locus as of the instant application's priority date. "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." [MPEP §2164.01, citing *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n, 1983)] Appellant submits that modification of factors such as primer sequence, salt concentration, temperature, denaturing agents, *etc.* were typically engaged in by those practicing amplification techniques.

2. *The Asserted "Art-Recognized Issue" With Amplification of HLA Loci is Not Relevant to the Instant Claims*

Paragraphs 23 and 24 of the Final Action cite the references of Canck *et al.* (U.S. 2002/0197613 A1) and Baxter-Lowe *et al.* (6,194,147) to assert that there were art-recognized issues with amplifying HLA loci. Appellant initially notes that neither of those references was available as of the instant application's priority date. This appears to conflict with the requirement that the specification must be enabling as of the application's filing date. [MPEP §2164.05] "Whether the specification would have been enabling as of the filing date involves consideration of the nature of the invention, the state of the prior art, and the level of skill in the art." [*Id.*] "The state of the prior art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains. The relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains at the time the application was filed." [*Id.*] Thus, it is clear that enablement is to be judged as of the application's filing (or priority) date, against the backdrop of the knowledge and skill in the art as of that date. "In general, the examiner should not use post-filing date references to demonstrate that the patent is non-enabling." [*Id.*]

This is not a situation in which a later publication states that a claimed invention could not be achieved. In fact, both of the cited publications claim methods for HLA typing by PCR amplification, thus acknowledging that PCR amplification of HLA loci is possible.

The citation to Canck *et al.* is inappropriate, as that reference concerned HLA typing by analyzing exon sequences of the HLA loci. The claimed methods of the instant application concern haplotyping of HLA loci by examining non-coding region sequences. The Specification makes clear that because non-coding regions are more informative than coding regions, the length of amplified sequences needed is shorter. For example:

> Addition of invariant exon sequences provides no additional genetic variation. When about eight or more alleles are to be distinguished, as for the DQA1 locus and more variable loci, amplified sequences should extend into at least one intron in the locus, preferably an intron adjacent to the variable exon.
>
> Additionally, where alleles of the locus exist which differ by a single basepair in the variable exon, intron sequences are included in amplified sequences to provide sufficient variability to distinguish alleles. For example, for the DQA1 locus (with eight currently recognized alleles) and the DPB locus (with 24 alleles), the DQA1.1/1.2 (now referred to as DQA1 0101/0102) and DPB2.1/4.2 (now referred to as DPB0201/0402) alleles differ by a single basepair. To distinguish those alleles, amplified sequences which include an intron sequence region are required. About 300 to 500 nucleotides is sufficient, depending on the location of the sequence. That is, 300 to 500 nucleotides comprised primarily of intron sequence nucleotides sufficiently close to the variable exon are sufficient. [Specification at pg. 14, lines 15-35]

It is because the method of Canck *et al.* is directed to analysis of variations in exon sequences that it requires amplification of large, difficult to amplify amplicons. This point is emphasize in the passage cited by the Examiner:

> In addition, due to the emergence of new HLA-Class I alleles, certain allele combinations cannot be distinguished anymore by the detection of polymorphisms only in exon 2 and exon 3 and additional typing in exon 4 is required. This raises the need for the additional amplification of exon 4, resulting in an even larger amplicon. (Final Action at ¶23, emphasis added)

The cited passage refers to HLA typing only by analyzing polymorphisms in exons, not in non-coding regions. If anything, the disclosure of Canck *et al.* points out the novelty, utility and advantage of the instant claimed methods. To use the difficulties of Canck *et al.* in amplifying large exon sequences to infer that the shorter amplified non-coding region sequences of the instant claims would require undue experimentation is unjustified and inappropriate. Because the instant claimed methods utilize the higher information content present in non-coding sequences to determine haplotypes, they do not require amplification of large target sequences that are needed for analysis based solely on exon sequences. While the claimed methods do not

exclude analysis of coding region sequences in addition to non-coding region sequences, the use of the non-coding sequences allows amplification and analysis of shorter amplicons than an exclusively exon-based analysis.

The Final Action's reliance on Baxter-Lowe *et al.* (U.S. 6,194,147) is similarly misplaced, as that reference also discloses probe sequences based on coding region polymorphisms, not non-coding ones. Table 3 of Baxter-Lowe clearly shows that the probe sequences used were designed to bind to coding regions, since that Table also provides the amino acid sequences encoded by the probes. The difficulty of using coding region probes for HLA typing is emphasized by the instant Specification at pg. 14, lines 21-24:

> Additionally, where alleles of the locus exist which differ by a single basepair in the variable exon, intron sequences are included in the amplified sequences to provide sufficient variability to distinguish alleles.

It is precisely that limited variability in exon sequences that is posed as a problem by Baxter-Lowe:

> Some of these sequences are closely similar, and vary by as little as a single nucleotide. The need for a typing method which can identify single nucleotide differences at single locations is apparent, although it should not be necessary to detect silent changes, i.e., mismatches which do not change the resulting amino acid. (6,194,147, col. 11, lines 39-45)

It is because the methods of de Canck *et al.* and Baxter-Lowe *et al.* are targeted at coding region sequence variations that they encountered difficulties. Because the instant claimed methods concern analysis of highly informative non-coding region sequences, the difficulties of analyzing highly conserved coding region sequences are overcome. For that reason, it is inappropriate to assert a lack of enablement of the instant application, based upon the non-analogous methods utilized by de Canck and Baxter-Lowe.

C. The Meaning of the Claims is Clear to a Person of Ordinary Skill in the Art

A response after final action was filed on June 30, 2004, to comply with requirements of form and to reduce the number of issues on appeal. Claim amendments were proposed to address each of the §112, second paragraph issues raised by the Final Action. Specifically, Claims 1, 13 and 19 were amended to recite "human leukocyte antigen" followed by the abbreviation "(HLA)". Claims 1, 13 and 19 were amended to delete "genetic coding" from the phrase "HLA genetic

coding locus". Claim 8 was amended to recite "a coding region of the locus" instead of "the coding region of the locus."

An Advisory Action mailed on July 16, 2004, refused entry of all proposed amendments because, "they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal." Appellant respectfully suggests that the amendments addressed to the 112, second paragraph rejections would in fact reduce or simplify the issues for appeal, as they would have eliminated some or all of the claim rejections under 112, second paragraph. In accordance with MPEP §1207, Appellant requests reconsideration and entry of the amendment.

1. The meaning of "HLA" is Clear

The Final Action asserted at ¶ 27 that claims 1, 13 and 19 are indefinite for their recitation of "HLA." Appellant asserts that the meaning of "HLA" is quite clear, as that abbreviation is defined at pg. 2, lines 24-25 as "human leukocyte antigen (HLA)."

2. The meaning of "HLA genetic coding locus" is Clear

The Final Action asserted at ¶ 28 that, "[c]laims 1,13 and 19 are indefinite with respect to just what constitutes the 'HLA genetic coding locus.'" The Final Action states that, "a locus, by definition, must already comprise a coding region" and asserts that, "it is unclear as to how a genetic coding locus is to be differentiated from a coding locus, or with simply a locus." [Final Action at ¶28]

As acknowledged in the Final Action, the Specification at pg. 11, lines 3-9 states that, "an HLA locus is the region of the genomic DNA that includes the gene that encodes an HLA gene product." The Specification at pg. 11, lines 3-7 defines the term "genetic locus" as, "the region of the genomic DNA that includes the gene that encodes a protein including any upstream or downstream transcribed non-coding regions and associated regulatory regions." Thus, the meaning of "an HLA genetic...locus" is clear from the Specification. The Final Action appears to assert that the insertion of the word "coding" into the phrase "an HLA genetic...locus" renders that phrase indefinite and raises the question of how "an HLA genetic locus" differs from "an HLA genetic coding locus."

According to the definitions of terms in the Specification, there is no difference between "an HLA genetic locus" and "an HLA genetic coding locus," as a "genetic locus" is defined to "include the gene that encodes a protein..." Therefore, since the meaning of "an HLA genetic locus" is clear from the Specification, the metes and bounds of "an HLA genetic coding locus" would be readily apparent to the skilled artisan. Appellant notes that an amendment after final to remove the words "genetic coding" from the phrase "an HLA genetic coding locus" was refused entry as not materially reducing or simplifying the issues for appeal.

3. *The phrase "the coding region of the locus" does not lack antecedant basis.*

The Final Action asserts at ¶29 that the phrase "the coding region of the locus" lacks antecedent support. However, "[t]his form paragraph should ONLY be used in aggravated situations where the lack of antecedent basis makes the scope of the claim indeterminate." [MPEP §706.03(d)] Obviously, "the failure to provide explicit antecedent basis for terms does not always render a claim indefinite. If the scope of a claim would be reasonably ascertainable by those skilled in the art, then the claim is not indefinite. *Ex parte Porter*, 25 USPQ2d 1144, 1145 (Bd. Pat. App. & Inter. 1992).... Inherent components of elements recited have antecedent basis in the recitation of the components themselves." [MPEP §2173.05]

Appellant asserts that antecedent basis for "the coding region of the locus" is found in the claim 1 recital of "human HLA genetic coding locus." As discussed above, the Specification at pg. 11, lines 3-7 defines the term "genetic locus" as, "the region of the genomic DNA that includes the gene that encodes a protein including any upstream or downstream transcribed non-coding regions and associated regulatory regions." It follows from the definition of "genetic locus" that the presence of a "coding region of the locus" is inherent in the recitation of a "human HLA genetic coding locus." Thus, the "coding region of the locus" would consist of the region of the HLA genetic coding locus that "encodes a protein." Such a meaning would be clear to the skilled artisan and the phrase is therefore not indefinite. Appellant notes that an amendment after final to change "the coding region of the locus" to "a coding region of the locus" was refused entry as not materially reducing or simplifying the issues for appeal.

As for the question of whether "the coding region of the locus" would "encompass coding regions (exons) of other genes that are in genetic linkage with the locus" (Final Action at

¶29), Appellant fails to see any basis in the claim language or the Specification to support such a construction. The claim clearly recites "the coding region of the locus," not "the coding region of any gene in genetic linkage with the locus." The definition of "genetic locus" in the specification would also appear inconsistent with the Examiner's suggested construction, as it recites, "the region of the genomic DNA that includes the gene that encodes a protein including any upstream or downstream transcribed non-coding regions and associated regulatory regions." There is no recitation relevant to all genes in genetic linkage with the locus.

D. The Examiner Failed to Establish a *Prima Facie* Case of Obviousness to Support a Rejection Under 35 U.S.C. § 103(a).

The examiner bears the initial burden of establishing a *prima facie* case of obviousness [MPEP § 2142]. A *prima facie* case of obviousness requires: [1] some suggestion or motivation, either in the cited references or in the knowledge generally available in the art, to modify the reference or combine reference teachings; [2] a reasonable expectation of success in achieving the claimed invention; and [3] the prior art reference(s) must teach or suggest all the elements of the claimed invention. [*In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)] As discussed below, the Examiner has failed to provide factual support for each of the three requirements of a *prima facie* case of obviousness. In addition, the cited references actually "teach away" from the claimed methods.

1. No suggestion or motivation to combine the reference teachings was present in the cited references or in the knowledge generally available in the art.

In rejecting claims under 35 U.S.C. §103, the cited references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination, without the benefit of impermissible hindsight afforded by the claimed invention. [MPEP §2141] As discussed in the following section (2), not only do the cited references lack any suggestion of the desirability of making the claimed combination, but when considered as a whole they teach away from the claimed combination.

The Final Action states that, "Erlich, abstract, teaches a method for performing HLA typing..." but, "does not teach performing an amplification step." [Final Action at ¶¶ 34 and 37] The Final Action asserts that, "Woo et al., page 7, teaches performing an analysis of sample

DNA where mutations in non-coding and coding regions are evaluated. In particular, the mutation associated with phenylketonuria (PKU; applicant's claim 7)." [Final Action at ¶38] Woo et al. is also said to, "teach combining polymerase chain reaction with the method of nucleic acid analysis as such allows for detection of point mutations with greater ease as well as analysis of minute quantities of DNA." [Final Action at ¶40] The Final Action then asserts that, "In view of the teachings of the prior art, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Erlich with the amplification and detection method of Woo et al., so as to allow for the analysis of greater number of human HLA loci and the facile determination of mutations associated with a disease, or with an individual as it relates to paternity testing." [Final Action at ¶42]

The Final Action provides no citation to the prior art of record that suggests the desirability of making the claimed combination. "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggest the desirability of the combination." [MPEP §2143.01, citing *In re Mills*, 916 F.2d 680, USPQ2d 1430 (Fed. Cir. 1990] Rather than providing an explicit suggestion in the prior art of the desirability of making the claimed combination, the Examiner asserts without any evidentiary support that, "In view of the teachings of the prior art, it would have been obvious...to have modified the method of Erlich with the amplification and detection method of Woo et al...." [Final Action at ¶42]

Reliance on common knowledge in the art requires substantial evidence in support of the Examiner's conclusion. [MPEP § 2144.03] "Official notice unsupported by documentary evidence should only be taken by the examiner where the facts asserted to be well-known, or to be common knowledge in the art are capable of instant and unquestionable demonstration as being well known. [*Id.*, citing *In re Ahlert,* 424 F.2d 1088, 1091, USPQ 418, 420 (CCPA 1970)] "It is never appropriate to rely solely on 'common knowledge' in the art without evidentiary support in the record, as the principal evidence upon which a rejection was based." [*Id.,* citing *In re Zurko,* 258 F.3d 1379, 1385, 59 USPQ2d 1693, 1697 (Fed. Cir. 2001)] Appellant respectfully asserts that the Examiner's conclusion that "in view of the teachings of the prior art" it would have been obvious to combine Erlich with Woo et al. is without any documentary support in the cited prior art. The simple fact that it would have been possible to combine Erlich with Woo et

al., without some suggestion of the desirability of such a combination, is insufficient to establish a *prima facie* case of obviousness.

2. The Final Action fails to establish a reasonable expectation of success in achieving the claimed invention.

A *prima facie* case of obviousness requires that the establishment of a reasonable expectation of success in achieving the claimed invention. [*In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)] The reasonable expectation of success must be found in the cited prior art, not in the applicant's disclosure. [*Id.*]

A reasonable expectation of success has been found in the biological arts where a prior art reference, "contained a detailed enabling methodology, a suggestion to modify the prior art to produce the claimed invention, and evidence suggesting the modification would be successful." [MPEP §2143.02, citing *In re O'Farrell,* 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988] In the instant case, all three factors found in *O'Farrell* to support a conclusion of reasonable expectation of success are missing.

First, there is no "detailed enabling methodology" disclosed in the cited prior art. The sole disclosure relevant to polymerase chain reaction amplification is a prophetic example in Woo et al. (pages 24-27). That example provides only general guidance to the skilled artisan as to how to perform PCR amplification, with no disclosure of how such a technique might be applied to HLA loci. The Final Action takes the position that amplification primers and amplification conditions specific for HLA loci are required for enablement [*see* Final Action at ¶¶ 20-24] Neither Woo et al. nor Erlich provide <u>any</u> HLA primer sequences or amplification conditions for HLA loci. In contrast, the instant application discloses, according to the Final Action (¶16), primers specific for the HLA-A, HLA-B, HLA-C, Class I, HLA-DQA1, HLA-DRA, HLA-DRB, HLA-DQB1 and HLA-DPB1 loci. In fact, the instant application discloses fifty-eight specific HLA primer sequences (SEQ ID NO's 30-87), compared to <u>zero</u> HLA primers disclosed in the cited prior art. The instant application further provides numerous specific examples of the actual amplification and analysis of non-coding sequences from HLA loci, compared to a single prophetic example of Woo et al. which discloses non-working conditions for amplification. Specifically, Woo et al at pg. 25, 2nd ¶ state:

> One microgram of human DNA, 1 μM of each oligonucleotides and 1.5 mM of each deoxynucleotide triphosphate in 10 mM tris-chloride is heated at **100°C** for 5 minutes and cooled in an **ice bath**. Five units of Klenow fragment is added and the reaction is incubated at **25°C** for 2 minutes. The cycle of heating, cooling, adding enzyme and reacting is repeated twenty times. (emphasis added)

Appellant asserts that the person of ordinary skill, as of the instant application's priority date, would have been aware that the temperature conditions disclosed by Woo et al. were generally unsuitable for PCR amplification. For comparison, the instant application at pg. 79, lines 1-11 disclosed standard PCR amplification conditions:

> Each amplification reaction mixture is heated to 94°C for 30 seconds. The primers are annealed to the sample DNA by cooling the reaction mixtures to 65°C for each of the A locus-specific amplification mixtures and to 55°C for each of the DQA1 locus-specific amplification mixtures and maintaining the respective temperatures for one minute. The primer extension step is performed by heating each of the amplification mixtures to 72°C for one minute. The denaturation, annealing and extension cycle is repeated 30 times for each amplification mixture.

In the absence of enabling details concerning <u>any</u> primer sequences, along with marginal disclosure of amplification conditions, Appellant asserts that the cited prior art failed to disclose enabling methodology sufficient to provide a reasonable expectation of success in achieving the claimed invention.

As noted previously, no suggestion to modify the prior art, nor any evidence suggesting the modification would be successful, is cited by the Final Action. In fact, the cited prior art taught away from the claimed combination, by leading the skilled artisan to believe that the RFLP analysis used by Erlich for HLA typing was <u>undesirable</u>, compared to the direct detection of causal mutations by DNA sequencing and/or probe hybridization used by Woo et al. Woo et al. state at pg. 4, 1st paragraph that:

> These methods of heterozygote detection require the ascertainment of a family through a proband. Furthermore, they require family studies in order to determine the segregation of the PKU alleles with restriction fragment length polymorphisms (RFLP) at the phenylalanine hydroxylase (PAH) locus. Even with family studies, the extensive RFLP's identified in the human phenylalanine hydroxylase locus still leaves some families without a method for detection of heterozygosity or for prenatal diagnosis of affected PKU individuals. The present invention is directed to a new an improved use of molecular biology technology to measure the actual mutations in the PAH locus.

Thus, far from suggesting the claimed combination, the cited prior art actually taught away from the claimed combination, suggesting that the direct measurement of causal mutations was superior to indirect detection of linked RFLP sites. Considering the cited prior art references as a whole, in the absence of any suggestion to make the claimed combination, along with a teaching away from the claimed combination, renders the combination of references improper and fails to provide a reasonable expectation of success in achieving the claimed combination.

3. The Final Action fails to assert that the cited prior art teach or suggest all the elements of the claimed invention.

Nowhere does the Final Action assert that either Woo or Erlich teach the element of "using the one or more non-coding region sequence variations [detected in an amplified genomic DNA sequence] to determine at least one haplotype encompassing [a] human HLA genetic coding locus," as recited in pending Claim 1. Rather, the Final Action asserts that it would have been obvious to have modified the method of Erlich with the method of Woo et al. to allow for the "determination of mutations associated with a disease, or with an individual as it relates to paternity testing." [*Id.*] However, the pending claims do not contain any recitation of, "determination of mutations associated with a disease, or with an individual as it relates to paternity testing." Rather, the claims clearly refer to determining haplotypes encompassing HLA loci. As the Final Action fails to assert that the element of "using the one or more non-coding region sequence variants to determine at least one haplotype encompassing a human HLA locus is disclosed in either cited reference, a *prima facie* case of obviousness has not been established.

CONCLUSION

Appellant respectfully asserts that each of the rejections set forth in the Final Action is improper. The rejections under 35 U.S.C. §112, first paragraph for lack of written description and lack of enablement are based on a flawed construction of claim scope, that is inconsistent with the interpretation that those skilled in the art would reach, considering the clear language of the claims and the further disclosure of the Specification. Appellant asserts that there is ample written description support in the Specification, commensurate with the properly construed scope of the claims, and that the disclosure in the Specification, in consideration of general knowledge in the prior art, provides ample enablement support. Although the Examiner should properly have entered the requested amendment after final action, which would have addressed all

outstanding §112, second paragraph issues, Appellant asserts that the meaning of the presently pending claims would be clear to the skilled artisan.

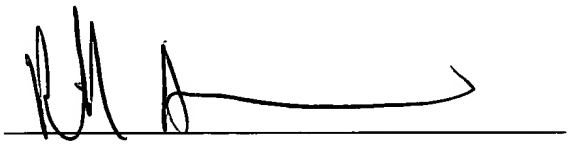
As discussed above, since the Examiner failed to establish a *prima facie* case of obviousness, including a lack of support for each of the three *In re Vaeck* factors required for a *prima facie* case, the rejection of claims under 35 U.S.C. §103 was also improper.

Appellant respectfully requests that: (a) the previously submitted amendment after final be entered in the case; and (b) reversal of the Examiner's rejections and allowance of the pending claims.

The appropriate fee for the 5-month extension is enclosed. Should any additional fee be required, the Commissioner is authorized to charge our Deposit Account No. 06-0029 and requested to notify us of same.

Respectfully submitted,
FAEGRE & BENSON LLP

Date: July 18, 2005



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APPENDIX A

37 C.F.R. § 1.192(c)(9)

The claims on appeal read as follows:

Claim 1. (previously presented) A method of determining at least one haplotype encompassing a human HLA genetic coding locus comprising:

(a) amplifying human genomic DNA, wherein the amplified genomic DNA comprises a non-coding region sequence that is in genetic linkage with an HLA genetic coding locus;

(b) detecting one or more sequence variations in the non-coding region; and

(c) using the one or more non-coding region sequence variations to determine at least one haplotype encompassing the human HLA genetic coding locus.

Claim 2. (original) The method of claim 1, wherein a single haplotype is determined.

Claim 3. (original) The method of claim 1, wherein two or more haplotypes are determined.

Claim 4. (canceled)

Claim 5. (original) The method of claim 1, wherein the at least one haplotype is associated with a genetic disease.

Claim 6. (original) The method of claim 5, wherein the disease is cystic fibrosis.

Claim 7. (original) The method of claim 5, wherein the disease is phenylketonuria, muscular dystrophy or beta-thalassemia.

Claim 8. (previously presented) The method of claim 1, further comprising

(i) detecting one or more sequence variations in the coding region of the locus; and

(ii) using the one or more coding region sequence variations to determine at least one haplotype encompassing the human HLA genetic coding locus.

Claim 9. (previously presented) The method of claim 1, further comprising:

(a) analyzing DNA from a crime scene sample;

(b) analyzing DNA from a sample of a suspected perpetrator of the crime; and

(c) comparing the haplotypes present in the crime scene sample and the suspected perpetrator sample.

Claim 10. (canceled)

Claim 11. (previously presented) The method of claim 1, further comprising:

(a) analyzing DNA from an off-spring;

(b) analyzing DNA from at least one suspected parent; and

(c) comparing the haplotypes present in the offspring's DNA and in the suspected parent's DNA.

Claim 12. (original) The method of claim 1, wherein the amplified genomic DNA further comprises at least part of at least one exon.

Claim 13. (previously presented) A method for determining at least one haplotype encompassing a multi-allelic human HLA genetic coding locus comprising:

(a) amplifying human genomic DNA with a primer pair that spans a non-coding region sequence, said primer pair defining a DNA sequence which is in genetic linkage with said HLA genetic coding locus and contains a sufficient number of non-coding region sequence nucleotides to produce an amplified DNA sequence characteristic of said at least one haplotype;

(b) analyzing the amplified DNA sequence to detect one or more sequence variations in the non-coding region; and

(c) using the one or more non-coding region sequence variations to determine at least one haplotype encompassing the multiallelic human HLA genetic coding locus.

Claim 14. (original) The method of claim 13, wherein a single haplotype is determined.

Claim 15. (original) The method of claim 13, wherein two or more haplotypes are determined.

Claim 16. (canceled)

Claim 17. (original) The method of claim 13, wherein the at least one haplotype is associated with a genetic disease.

Claim 18. (original) The method of claim 17, wherein the genetic disease is associated with variations in a regulatory or other untranslated region of the genetic locus.

Claim 19. (previously presented) A method for determining at least one haplotype encompassing a human HLA coding locus comprising:

(a) amplifying human genomic DNA with a primer pair that spans a non-coding region sequence, said primer pair defining a DNA sequence which is in genetic linkage with said HLA coding locus;

(b) analyzing the amplified DNA sequence to detect one or more sequence variations in the non-coding region; and

(c) using the one or more non-coding region sequence variations to determine at least one haplotype encompassing the human HLA coding locus.

Claim 20. (original) The method of claim 19, wherein a single haplotype is determined.

Claim 21. (original) The method of claim 19, wherein two or more haplotypes are determined.

Claim 22. (canceled)

Claim 23. (previously presented) The method of claim 19, further comprising:

(a) analyzing DNA from a crime scene sample;

(b) analyzing DNA from a sample of a suspected perpetrator of the crime; and

(c) comparing the haplotypes present in the crime scene sample and the suspected perpetrator sample.

Claim 24. (canceled)

Claim 25. (previously presented) The method of claim 19, further comprising:

(i) analyzing DNA from an off-spring;

(ii) analyzing DNA from at least one suspected parent; and

(iii) comparing the haplotypes present in the offspring's DNA and in the suspected parent's DNA.

Claim 26. (previously presented) The method of claim 1, wherein the haplotype is determined by detecting polymorphisms in coding and non-coding regions.

Claim 27. (previously presented) The method of claim 1, wherein the non-coding region comprises an intervening sequence, a 5' untranslated sequence (5'-UTR), a 3'-UTR, a regulatory sequence or an intergenic sequence.

Claim 28. (previously presented) The method of claim 13, wherein the non-coding region comprises an intervening sequence, a 5' untranslated sequence (5'-UTR), a 3'-UTR, a regulatory sequence or an intergenic sequence.

Claim 29. (previously presented) The method of claim 19, wherein the haplotype is determined by detecting polymorphisms in coding and non-coding regions.

Claim 30. (previously presented) The method of claim 19, wherein the non-coding region comprises an intervening sequence, a 5' untranslated sequence (5'-UTR), a 3'-UTR, a regulatory sequence or an intergenic sequence.

Claims 31-46. (canceled)

NOT FOR CITATION

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

GENETIC TECHNOLOGIES LTD.,

Plaintiff,

v.

APPLERA CORPORATION,

Defendant.

/

No. C 03-1316 PJH

CLAIM CONSTRUCTION ORDER

A claim construction hearing to construe the disputed terms of U.S. Patent Nos. 5,621,179 ("'179 patent") and 5,851,762 ("'762 patent") pursuant to Markman v. Westview Instruments, Inc., 517 U.S. 370 (1996), was held on September 1, 2004 before this court. Plaintiff appeared through its counsel Felicia Boyd and Natalie Hanlon-Leh, and defendant appeared through its counsel Nicholas Groombridge and John Garretson. Having read the parties' papers and carefully considered their arguments and the relevant legal authority, the court hereby rules as follows.

BACKGROUND

Plaintiff Genetic Technologies Ltd. ("GTG") is the assignee for the '179 and '762 patents, both of which cover methods of analyzing non-coding portions of DNA.

Each organism's unique genetic information is stored in its DNA. Genes are located along a DNA strand, and control that organism's traits, such as eye color or hair color. An allele is defined as the different types of traits that are possible with a certain type of gene, so if the gene controls eye color, for instance, the alleles could be blue, brown, or green. A haplotype, in comparison, is a tendency for certain alleles to be inherited together, such as blond hair and blue eyes, or red hair and green eyes.

DNA consists of two strands of proteins connected by protein base pairs in a double helix form. These strands are to be read in a certain direction, with the beginning of the DNA strand designated as the 3' end and the end of the strand designated as the 5' end. Groups of proteins in the DNA strand, or genes, can be transcribed and translated by the cell into instructions to create other proteins, which yield certain traits. DNA is stored in the nucleus of the cell, in compacted forms known as chromosomes.

Genes themselves contain various subregions. Only the region known as the exon contains actual instructions on protein coding. Other portions of the gene are copied in the beginning of the transcription process, but are ultimately deleted before translation of the gene into protein coding instructions begin. These "non-coding" portions include sections known as "introns," "untranslated regions" ("UTRs"), and "intergenic regions." UTRs are further designated as either 3' UTRs or 5', to indicate the direction of the DNA strand. Scientific discovery is ongoing with respect to the non-coding portions and it is possible that new regions will be designated and named later.

Previously, these non-coding DNA regions were considered of no scientific interest in molecular biology. However, the discovery at issue in these two patents is that the non-coding regions in fact contain information that correlates with certain genetic traits. So, for instance, the gene that causes cystic fibrosis might be correlated with a certain specific protein string in the deleted regions, so it would be possible to determine whether a person carried that gene by analyzing whether a certain protein string could be found in the non-coding regions of their DNA.[1]

The patents thus cover methods of discovering whether or not a certain protein string exists in a DNA strand, either to detect an allele or group of alleles, or to locate where on a chromosome an allele or group of alleles can be found. To do so, the scientist first makes copies of the DNA strand in question, in a process known as "amplification." After the DNA strand is amplified, various different methods for analyzing the strands can be used to find

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[1] None of the examples provided in this order are to be taken as scientific fact, and those examples provided by the court may even be wrong.

certain information. The '179 patent covers a method of analysis by which strands are compared with other known strands to determine whether the strand at issue contains a certain allele. The '762 patent, in comparison, covers a method of analysis where the strands are analyzed to determine where on the chromosome the gene controlling the trait in question can be found, also through comparison between the strand in question and DNA from the general population.

DISCUSSION

A. Legal Standards

In construing claims, the court must begin with an examination of the claim language itself. "The terms used in the claims bear a 'heavy presumption' that they mean what they say and have the ordinary meaning that would be attributed to those words by persons skilled in the relevant art." Texas Digital Sys., Inc. v. Telegenix, Inc., 308 F.3d 1193, 1202 (Fed. Cir. 2002) (citations omitted), cert. denied, 123 S.Ct. 2230 (2003). See also Renishaw PLC v. Marposs Societa' per Azioni, 158 F.3d 1243, 1248 (Fed. Cir. 1998) ("The claims define the scope of the right to exclude; the claim construction inquiry, therefore, begins and ends in all cases with the actual words of the claim."). In determining ordinary meaning, the court is explicitly permitted to rely on reference materials such as dictionaries, treatises, or encyclopedias in general use on the date of the patent's issuance. Texas Digital, 308 F.3d at 1202-03 (citations omitted).

The words in the claim must then be interpreted "in light of the intrinsic evidence of record, including the written description, the drawings, and the prosecution history, if in evidence." Teleflex, Inc. v. Ficosa North Am. Corp., 299 F.3d 1313, 1324-25 (Fed. Cir. 2002) (citations omitted). "Such intrinsic evidence is the most significant source of the legally operative meaning of disputed claim language." Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed. Cir. 1996).

A patentee is presumed to have intended the ordinary meaning of a claim term in the absence of an express intent to the contrary. York Products, Inc. v. Central Tractor Farm & Family Ctr., 99 F.3d 1568, 1572 (Fed. Cir. 1996). Furthermore, "unless compelled otherwise,

a court will give a claim term the full range of its ordinary meaning as understood by persons skilled in the relevant art." Texas Digital, 308 F.3d at 1202 (citations omitted).

Intent to limit the scope of a claim, despite apparently-broad language, can be shown in four ways. First, if the patentee "acted as his own lexicographer," and clearly set forth a definition of the disputed term in either the specification or the prosecution history, the court will defer to that definition. CCS Fitness, Inc. v. Brunswick Corp., 288 F.3d 1359, 1366 (Fed. Cir. 2002) (citations omitted). Second, the court will alter the ordinary meaning of a term "if the intrinsic evidence shows that the patentee distinguished that term from prior art on the basis of a particular embodiment, expressly disclaimed subject matter, or described a particular embodiment as important to the invention." Id. at 1367. Third, a claim term will not take its ordinary meaning "if the term chosen by the patentee so deprives the claim of clarity as to require resort to the other intrinsic evidence for a definite meaning." Id. Finally, a term in a step- or means-plus-function claim is limited by statute to the structure or step described in the embodiment. 35 U.S.C. § 112 ¶ 6.

Limitations from the specification, such as from the preferred embodiment, cannot be read into the claims absent an express intention to do so. Teleflex, 299 F.3d at 1326 ("The claims must be read in view of the specification, but limitations from the specification are not to be read into the claims.") (citations omitted); CCS Fitness, 288 F.3d at 1366 ("a patentee need not describe in the specification every conceivable and possible future embodiment of his invention."); Altiris v. Symantec Corp., 318 F.3d 1363, 1372 (Fed. Cir. 2003) ("resort to the rest of the specification to define a claim term is only appropriate in limited circumstances"). To protect against this, the court should not consult the intrinsic evidence until after reviewing the claims in light of the ordinary meaning of the words themselves. Texas Digital, 308 F.3d at 1204-05 (to act otherwise "invites a violation of our precedent counseling against importing limitations into the claims") (citations omitted).

Only if an analysis of the intrinsic evidence fails to resolve any ambiguity in the claim language may the court then rely on extrinsic evidence, such as expert declarations. Vitronics, 90 F.3d at 1583 ("In those cases where the public record unambiguously describes the scope

of the patented invention, reliance on any extrinsic evidence is improper").

B. '179 Patent

Five terms are at issue in the '179 patent.

1. "Non-Coding Region Sequence"

GTG proposes the definition "any untranslated DNA sequences, such as sequences between exons, the 5' and 3' untranslated regions, and sequences between genetic loci." Applera proposes "all non-exon sequences, including sequences between exons, the 5' and 3' untranslated regions, and sequences between genetic loci." The parties agree that the definitions' examples of untranslated DNA sequences are accurate, but dispute whether the term "untranslated DNA sequences" or "non-exon sequences" better describes the regions at issue.

In the prosecution of the '179 patent, the applicant conceded that the term "non-coding region sequence" should be substituted for the term "intron" throughout the claims, because the applicant was using the term "intron" in a broader sense than its then-accepted definition at the time. GTG Exh. E at 58227 (Sept. 23, 1992 Preliminary Amendment). Thus, the specification states:

> As used herein, the term "intron" refers to untranslated DNA sequences between exons, together with 5' and 3' untranslated regions associated with a genetic locus. In addition, the term is used to refer to the spacing sequences between genetic loci (intergenic spacing sequences) which are not associated with a coding region and are colloquially referred to as "junk." While the art traditionally uses the term "intron" to refer only to untranslated sequences between exons, this expanded definition was necessitated by the lack of any art recognized term which encompasses all non-exon sequences.

'179 patent col. 5:40-50.

GTG argues that its definition is more accurate than Applera's, because at the time the patent issued, the 5' and 3' UTRs were considered exons, see, e.g., GTG Exhs. U, V (biology texts defining 5' and 3' sections as exons), and it would thus be inconsistent to define the term "non-exon sequences" as including an exon sequence.[2] Texas Digital, 308 F.3d at 1202-03

[2] The analogy provided at the hearing was that it would be inconsistent to proffer a definition such as "non-shoe objects, including trucks, cars, and stilettos," since stilettos are a type of shoe and it would be inconsistent to define a shoe as a "non-shoe object."

(dictionaries in use at the time of the patent's issuance may be relied upon in construing a claim). The court agrees with GTG. The term is thus construed as: **any untranslated DNA sequences, such as sequences between exons, the 5' and 3' untranslated regions, and sequences between genetic loci.**

2. "Spans [a Non-Coding Region Sequence]"

The parties agree that the term "spans" can be construed as "amplifies." However, Applera argues that the term "spans a non-coding region sequence" must be further limited to encompass the further requirement that the sequence in question include introns as non-conserved DNA sequences. GTG argues that no limitation is necessary.

A conserved sequence is one which does not vary significantly between individuals. Thus, if a conserved sequence is included in the non-coding region of the DNA to be analyzed, that section will not show any significant differences between the strand in question and the other strands used in comparison. Thus, non-conserved sections must also be included in the DNA region analyzed in order to find the necessary variations between the strand under analysis and the comparator strands to perform the method described in the patent.

Applera argues that because the specification defines a "non-coding" region as synonymous with the term "intron," and because the specification defines the term "intron-spanning primer" as spanning non-conserved regions, the term "spans" must require that non-conserved sequences be included in a non-coding region sequence. However, nothing in the claims or prosecution history implies that the description in the specification for "intron-spanning primer" should be imported into the claim interpretation for the term "spans," and thus to do so would be improper. See Texas Digital, 308 F.3d at 1204-05; Teleflex, 299 F.3d at 1326. The term "spans" is thus construed as: **amplifies**, with no further limitation that the region spanned must include a non-conserved intron section.

3. "In Genetic Linkage"

GTG proposes that the term "in genetic linkage" be construed as "a tendency of DNA sequences on the same chromosome to be linked together," and Applera proposes "DNA

sequences that are on the same chromosome and are inherited together." Both parties agree that the dictionary definition of the term "genetic linkage" requires only a tendency for traits to be inherited together. However, Applera claims that prosecution history estoppel limits the breadth of the claims.

Prosecution history estoppel only occurs when a patentee clearly and unmistakably disavows the breadth of a claim. See, e.g., Omega Eng'g Inc. v. Raytek Corp., 334 F.3d 1314, 1326 (Fed. Cir. 2003). While the statement that "DNA sequences which are in genetic linkage are regions of genomic DNA that are inherited together" in the prosecution history could potentially be read as stating that 100% certainty of linkage is necessary, see Applera Exh. L at 5, that reading does not demonstrate the necessary "clear and unmistakable surrender" of subject matter for that reading of the prosecution history to apply. Cordis Corp. v. Medtronic AVE, Inc., 339 F.3d 1352, 1359 (Fed. Cir. 2003), cert. denied, 124 S. Ct. 1426 (2004).

Furthermore, the next sentence of that section of the prosecution history reaffirms that "[s]ince the meaning of the term 'genetic linkage' is well known in the art and is used in the specification and claims in a manner consistent with that definition, the meaning of the claims is clear." Applera Exh. L. at 5. On this record, Applera cannot show "clear and unmistakable" intent to require 100% certainty of linkage beyond the dictionary definition of the term.

The court thus adopts GTG's definition, and construes the term "in genetic linkage" as: **a tendency of DNA sequences on the same chromosome to be linked together**.

4. "Characteristic of Said Allele"

GTG originally proposed the definition "capable of distinguishing at least one allele from at least one other allele. More than one amplified DNA sequence may be used for loci where alleles differ by single nucleotide substitutions that are not unique to the allele or when information regarding remote alleles (haplotypes) is desired." At the claim construction hearing, GTG modified its definition to simply "capable of distinguishing at least one allele from at least one other allele." Applera proposes "a trait, quality, or property that is unique." Following the hearing, GTG submitted a subsequent modification to its definition to: "a trait,

quality, or a group of them distinguishing an individual, group, or type."

GTG is correct that the prosecution history does not limit the claims to a construction where a one-to-one correspondence has been demonstrated between the DNA sequences and the allele in question, nor does it imply "uniqueness," as Applera argues. When read in context, it is clear that the one-to-one correlation described in both the prosecution history and the specification is merely provided as an example and is not intended to limit the scope of the claims. Id.; Applera Exh. N at 19; '179 patent col. 7:24-28. However, Applera is correct that nothing in the claims or prosecution history requires that the term "characteristic" be given a construction other than its standard definition of "a trait, quality, or property or a group of them, distinguishing an individual, group, or type," as set forth in the prosecution history. Applera Exh. L at 5. GTG appears to have acknowledged this in their post-hearing proposed construction.

Accordingly, as between GTG and Applera, GTG's final proposal is the most accurate. The court thus adopts GTG's construction of the term "characteristic of said allele" as: **a trait, quality or property, or a group of them, distinguishing an individual, group, or type.**

5. "To Determine"

GTG proposes the construction "to conclude or ascertain," while Applera proposes "to fix conclusively or authoritatively." The main dispute is whether the analysis of the DNA strand must be absolutely correct to fall within the scope of the claims.

Nothing in the dictionary definition of the term "to determine" implies that the determination must be 100% accurate, and nothing in the claims, specification, or prosecution history indicates any intent to limit the patent in that fashion. The term "to determine" is construed as: **to conclude or ascertain.**

B. '762 Patent

Ten terms are at issue in the '762 patent, though several terms were previously construed in the context of the '179 patent.

1. "To Identify"

The main dispute over this term concerns whether the preamble of the patent should be

read as a limitation on the claim. GTG argues that the preamble does not limit the claim, and the claim need not be construed. Applera argues that the preamble should be construed, and proposes the construction "establishing the identity of."[3]

Claims are only limited by the preamble if the preamble "recites essential structure or steps, or if it is necessary to give life, meaning, and vitality to the claim." Catalina Marketing Int'l, Inc. v. Coolsavings.com, Inc., 289 F.3d 801, 808 (Fed. Cir. 2002) (citation omitted). In contrast, if the patent claims define "a structurally complete invention in the claim body," and the preamble is used "only to state a purpose or intended use of the invention," the preamble cannot be used to limit the claims, "unless there is clear reliance on the preamble during prosecution to distinguish the claimed invention from the prior art." Intertool, Ltd. v. Texar Corp., 369 F.3d 1289, 1295 (Fed. Cir. 2004), citing Catalina, 289 F.3d at 808.

Here, the preamble merely sets forth the purpose of claim 1 of the '762 patent, which is to outline a method for identifying markers and using the markers to find chromosomal regions. The claims themselves do not rely on the statement of purpose in any way, and do not rely on that definition of "identify" in setting forth the method at issue. Furthermore, there is no indication in the prosecution history that the applicant relied in any way on the use of the term "identify" in the preamble to distinguish the invention from the prior art. There is thus no reason to find the preamble limiting on the claims in this patent, and the court declines to construe the term.[4]

2. "Non-Coding Sequence"

Both parties agree that this term should be construed identically to "non-coding region sequence" in the '179 patent. "Non-coding sequence" is construed as: **any untranslated DNA sequences, such as sequences between exons, the 5' and 3' untranslated**

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[3] The verb "identify" appears in a number of places throughout both the preamble to claim 1 and the claims themselves, but the parties appear to focus solely on the use of the specific term "to identify" at col. 37:43-44.

[4] The term "identify" will thus be given its ordinary meaning when reading the claim, which in practice will result in a reading consistent with Applera's proposed dictionary definition of the term.

regions, and sequences between genetic loci.

3. "To Determine"

The parties proffer the same constructions and repeat their previous arguments concerning this term as it appeared in the '179 patent. The court construes "to determine" identically to its construction in the '179 patent, as: **to conclude or ascertain**.

4. "Haplotypic Pattern"

GTG proposes the construction "data, from an analytical method, that is characteristic of a particular haplotype." Applera proposes "a pattern of DNA fragments that have been separated according to mobility and visualized, and which is uniquely indicative of the presence of a particular haplotype," based on its reading of the prosecution history.

While it is true that in the prosecution history of the '762 patent, the patent examiner found the previously-proposed claims overbroad and unsupported by the specification, Applera Exh. U at 4, those findings were in relation to claims that did not contain the term "haplotypic pattern" but merely stated generally that a locus would be "identified." See, e.g., Applera Exh. S at 68. Those claims were then cancelled and newer, more specific claims describing the type of identification to be made, involving "haplotypic patterns," were substituted in their place on January 2, 1997. GTG Exh. N (also located at Applera Exh. W). Based on this file history, it is clear that GTG has not disclaimed coverage for haplotypic patterns that are not visualized, and that the claim covers any identification made through the comparison of haplotypic patterns in any way.

Furthermore, nothing in the specification or prosecution history implies that the identification made must be "uniquely indicative" of a particular haplotype, so that element of Applera's proposed construction is incorrect as well.

The court thus adopts GTG's construction, and construes the term "haplotypic pattern" as: **data, from an analytical method, that is characteristic of a particular haplotype**, without requiring that the data identify a haplotype to 100% accuracy or further specifying the analytical methods to be used.

5. "Selected Technique"

GTG proposes the construction "any analytical method chosen to detect haplotypic patterns," while Applera proposes "a method that produces patterns of DNA fragments that have been separated according to mobility and visualized, meaning RFLP analysis, primer defined length polymorphism and allele- and haplotype-specific amplification analysis."

The court adopts GTG's proposed construction. As previously discussed in the context of the term "haplotypic patterns," the prosecution history does not support Applera's interpretation of the claim as limiting the patent to two specific analytic methods. The term "selected technique" is construed as: **any analytical method chosen to detect haplotypic patterns**.

6. "Marker for a Haplotype"

GTG proposes the construction "indicator for a haplotype," and Applera proposes "a haplotypic pattern which uniquely identifies a haplotype."

The court adopts GTG's proposed construction. For the reasons stated previously, the patent and the prosecution history do not require that the haplotypic pattern "uniquely" identify the haplotype in question. The term "marker for a haplotype" is construed as: **indicator for a haplotype**.

7. "To Identify the Haplotype"

GTG proposes the construction "to establish as being a particular haplotype," and Applera proposes "to establish the identity of a unique haplotype."

The court adopts GTG's proposed construction. As previously stated, nothing in the patent or prosecution history indicates that the haplotypes must be uniquely identified. The term "to identify the haplotype" is construed as: **to establish as being a particular haplotype**.

8. "Subseries of Adjacent Selected Chromosomal Regions"

GTG proposes the construction "a successive subset of chosen chromosomal regions," and Applera proposes "a subseries of selected chromosomal regions within the same locus or, for intron DNA sequences not associated with a genetic locus, immediately preceding or

following the locus."

The construction of this claim is a close call, but GTG's arguments are slightly more persuasive than Applera's. The claim language here is admittedly ambiguous as to whether the subseries covers chromosomal regions that are adjacent to one another within a selected series of regions (GTG's proposal), or chromosomal regions that are adjacent to one another on the DNA strand before they are selected (Applera's proposal). In this circumstance, the court may properly rely on the specification to clarify the language. See, e.g., CCS Fitness., 288 F.3d at 1367.

The specification describes a method by which individual haplotypic regions on the DNA strand, separated by anywhere from .01 to 2 million DNA base pairs, are selected and analyzed. See '762 patent col. 13:7-21 (after one region is analyzed, the next haplotypic region appearing on the DNA strand is analyzed to create a map of "contiguous overlapping haplotypic regions."). In contrast, there is no description in the specification supporting Applera's interpretation of the claim that a continuous section of DNA is first selected, and then a second continuous subsection is then selected from within the first selected section.

While Applera proposes a plausible reading of what appears to be a rather poorly-drafted claim, when looking at the claim language in the context of the specification, the court is persuaded that GTG's position better describes the intended steps of the method described. Teleflex, 299 F.3d at 1324-25 (citations omitted). However, the court finds that GTG's construction is not entirely clear either. The court thus construes the disputed term as follows: **a group of chromosomal regions identified by the following process: Chromosomal regions on a DNA strand are selected. The regions need not be adjacent to each other on the DNA strand. The selected regions are then arranged in the order in which they appear on the DNA strand. Regions that are next to one another in this reconfiguration are then selected to comprise a group.**

The court acknowledges that this construction, while simplistic, may be imprecise. Accordingly, the court offers the parties the opportunity to stipulate to an alternate construction that embodies the court's basic finding that the chromosomal regions in question need not be

adjacent to one another on the actual DNA strand. Any stipulation shall be submitted no later than one week after the filing of this order. If the parties are unable to reach an agreement, the court's construction will be the final construction of this claim.

9. "Indication"

GTG proposes this term be construed as "suggestion or sign of," while Applera proposes "positive identification of said central selected chromosomal region as being associated with the trait."

The court adopts GTG's position. As previously discussed, the patent and prosecution history do not require "positive identification" of the region in question. "Indication" is thus construed as: **suggestion or sign of.**

10. "Analyzing Said Plurality of Amplified DNA Sequences"

GTG proposes the construction "observing any variation in the DNA sequence using any technique," and Applera proposes "applying the selected technique to said plurality of amplified DNA sequences."

The court adopts GTG's position. There is no indication in the claim language that limits the type of analysis that may be performed. Applera's proposed construction improperly imports limitations from the specifications into the claims. Texas Digital, 308 F.3d at 1204-05; Teleflex, 299 F.3d at 1326. The term is thus construed as: **observing any variation in the DNA sequence using any technique.**

The parties are ordered to submit a joint case management status report pursuant to Patent Standing Order ¶ 13 within 21 days of the filing of this order. The court will review the report and contact the parties if a further case management conference is needed. This order fully adjudicates the matter listed at no. 65 on the clerk's docket for this case.

IT IS SO ORDERED.

Dated: September 15, 2004

/s/
PHYLLIS J. HAMILTON
United States District Judge

NOT FOR CITATION

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

GENETIC TECHNOLOGIES LTD.,

Plaintiff,

v.

APPLERA CORPORATION,

Defendant.

_____/

No. C 03-1316 PJH

ORDER AMENDING CONSTRUCTION OF TERM "IN GENETIC LINKAGE"

Before this court is plaintiff Genetic Technology Ltd.'s September 17, 2004 letter noting a typographical error in the construction of the term "in genetic linkage" in the court's claim construction order of September 15, 2004. The court hereby corrects the construction of the term "in genetic linkage" and construes that term as "a tendency of DNA sequences on the same chromosome to be inherited together."

IT IS SO ORDERED.

Dated: September 23, 2004

_____/s/_____
PHYLLIS J. HAMILTON
United States District Judge

US Patent No. 5,612,179
INTRON SEQUENCE ANALYSIS METHOD FOR DETECTION OF ADJACENT AND REMOTE LOCUS ALLELES AS HAPLOTYPES

Claim Language (Construed Terms in Bold)	Joint Construction or	
	Plaintiff's Proposed Construction and Evidence in Support	Defendant's Proposed Construction and Evidence in Support
1. A method for detection of at least one coding region **allele** of a multi-allelic genetic locus comprising: **allele[s]** Found in claim numbers: '179 Patent: 1, 3, 4, 5, 7, 8, 9, 15, 24, 25, 26, 27, 28, 29, and 33	**allele** JOINT CONSTRUCTION: a sequence variation in a coding region EXHIBIT A No. C 03-1316 PJH (EDL)	
1. A method for detection of at least one coding region allele of a **multi-allelic** genetic locus comprising: **multi-allelic** Found in claim numbers: '179 Patent: 1, 9, and 26	**multi-allelic** JOINT CONSTRUCTION: known to have at least three alleles	
1. A method for detection of at least one coding region allele of a multi-allelic **genetic locus** comprising: **genetic locus** Found in claim numbers: '179 Patent: 1, 7, 8, 9, 14, 26, 27, 28, 30, and 31	**genetic locus** JOINT CONSTRUCTION: a region of genomic DNA that includes the coding region of the gene, the untranslated sequences of the gene and the sequences involved in regulating the gene	

Claim Language (Construed Terms in Bold)	Joint Construction or	
	Plaintiff's Proposed Construction and Evidence in Support	Defendant's Proposed Construction and Evidence in Support
a) **amplifying** genomic DNA with a primer pair that spans a non-coding region sequence, **amplifying** Found in claim numbers: '179 Patent: 1, 9, 19, 24, 25, 33, and 36	**amplifying** **JOINT CONSTRUCTION:** copying a nucleic acid sequence by any technique that utilizes a primer pair and results in an increase in the number of copies of the sequence to produce a sufficient amount of DNA for analysis	
a) amplifying **genomic DNA** with a primer pair that spans a non-coding region sequence, **genomic DNA** Found in claim numbers: '179 Patent: 1 and 9	**genomic DNA** **JOINT CONSTRUCTION:** chromosomal DNA	
a) amplifying genomic DNA with a **primer pair** that spans a non-coding region sequence, **primer pair** Found in claim numbers: '179 Patent: 1, 9, 19, 20, 21, 24, 33, and 36	**primer pair** **JOINT CONSTRUCTION:** a set of primers, including a 5' upstream primer that hybridizes with the 5' end of the DNA sequence to be amplified and a 3' downstream primer that hybridizes with the complement of the 3' end of the sequence to be amplified	
a) amplifying genomic DNA with a primer pair that **spans a non-coding region sequence,** **spans a non-coding region sequence** Found in claim numbers: '179 Patent: 1 and 9	**spans a non-coding region sequence** **PROPOSED CONSTRUCTION:** amplifies at least a portion of a non-coding region sequence **INTRINSIC EVIDENCE:** '239 application, Amendment dated 4/14/92, pp. 16-17 ("The exon/intron junction is a highly conserved portion of all interrupted genes since	**spans a non-coding region sequence** **PROPOSED CONSTRUCTION:** amplifies at least a portion of a non-coding region sequence, which includes sequences that are not conserved. **INTRINSIC EVIDENCE:** "The method comprises amplifying genomic DNA with a primer pair

Claim Language (Construed Terms in Bold)	Joint Construction or	
	Plaintiff's Proposed Construction and Evidence in Support	**Defendant's Proposed Construction and Evidence in Support**
	the region contains signals which are crucial for splicing of mammalian pre-mRNA. Accompanying this amendment is a copy of pages 639-640 of Molecular Biology of the Gene. Those pages detail that in mammalian genes like the phenylketonuria gene the sequences at the exon/intron boundaries are highly conserved. Therefore such sequences do not contain polymorphism that are indicative of the coding region alleles. The sequences therefore do not fall within the terms of the claims"); '179 patent col. 6: 10-15 ("The term 'intron-spanning primers', as used herein, means a primer pair that amplifies at least a portion of one intron, which amplified intron region includes sequences which are not conserved"); '179 patent. col. 8: 52-60 ("The amplified DNA sequence is located in a region of genomic DNA that contains genetic variation which is in genetic linkage with the allele to be detected. ... The sequence preferably includes at least a portion of one of the introns adjacent to a variable exon and can include a portion of the variable exon."); '652 application, Amendment dated 7/13/94, pg. 12, 2nd full paragraph ("At pg. 11, lines 31-33, the term 'intron spanning primers' is defined as 'a primer pair that amplifies at least a portion of one intron.' Therefore, since the primers amplify a portion of the intron, it is irrelevant whether the intron is 200 nucleotides or 10 kilobasepairs in length since the method only need amplify a portion of the intron.")	that spans an intron sequence and defines a DNA sequence in genetic linkage with an allele to be detected. Primer sites are located in conserved regions in the introns or exons bordering the intron sequence to be amplified." Col. 4:38-42. "The term "intron-spanning primers", as used herein, means a primer pair that amplifies at least a portion of one intron, which amplified intron region includes sequences which are not conserved." Col. 6:10-13. "The length of the amplified sequence which is required to include sufficient genetic variability to enable discrimination between all alleles of a locus bears a direct relation to the extent of the polymorphism of the locus (the number of alleles). That is, as the number of alleles of the tested locus increases, the size of an amplified sequence which contains sufficient genetic variations to identify each allele increases." Col. 7:34-41. "Defin[es]" a DNA sequence that "contains a sufficient number of non-coding region sequence nucleotides to produce an amplified DNA sequence characteristic of said allele." Col. 59:60-65.

Claim Language (Construed Terms in Bold)	Joint Construction or	
	Plaintiff's Proposed Construction and Evidence in Support	**Defendant's Proposed Construction and Evidence in Support**
a) amplifying genomic DNA with a primer pair that spans a **non-coding region sequence,** **non-coding region sequence[s]** Found in claim numbers: '179 Patent: 1, 2, 3, 6, 9, 17, 26, and 32	**non-coding region sequence** **PROPOSED CONSTRUCTION:** any untranslated DNA sequences, such as sequences between exons, the 5' and 3' untranslated regions, and sequences between genetic loci **DICTIONARY/TREATISE DEFINITIONS:** Webster's Medical Desk Dictionary (1986) (**noncoding** – "not specifying the genetic code"); Genes IV (1990), pgs. 484 & 810 (**exon** – "any segment of an interrupted gene that is represented in the mature RNA product"); Biology 5th Ed. (1999), pg. 303 (graphic showing the 3' and the 5' untranslated regions ("Poly (A) tail" and "5' Cap") as part of the exon) **INTRINSIC EVIDENCE:** '179 patent, col. 5: 40-50 ("As used herein, the term 'intron' refers to untranslated DNA sequences between exons, together with 5' and 3' untranslated regions associated with a genetic locus. In addition, the term is used to refer to the spacing sequences between genetic loci (intergenic spacing sequences) which are not associated with a coding region and are colloquially referred to as 'junk'. While the art traditionally uses the term 'intron' to refer only to untranslated sequences between exons, this expanded definition was necessitated by the lack of any art recognized term which encompasses all non-exon sequences"); '179 patent Abstract ("The method comprises amplifying genomic DNA with a primer pair	**non-coding region sequence** **PROPOSED CONSTRUCTION:** non-coding region sequence: the term "non-coding region sequence" means all non-exon sequences, including sequences between exons, the 5' and 3' untranslated regions, and sequences between genetic loci. **DICTIONARY/TREATISE DEFINITIONS:** Dictionary of Biochemistry and Molecular Biology, 2d Ed. (1989) p.164. "*exon*: A coding sequence in the DNA of eukaryotic genes. Such sequences are transcribed into RNA and are subsequently translated into protein. The term is also used for the translatable RNA sequence. Exons and introns (nontranslated, intervening sequences) make up split genes." coding: *Id.* p.88: "*coding DNA*: Sections of DNA that actually code for proteins or nontranslated RNAs such as tRNA and rRNA." Thus, non-coding region sequence is not synonymous with all nontranslated sequences. **INTRINSIC EVIDENCE:** non-coding region sequence: the term "non-coding region sequence" is synonymous with intron, as expressly defined in the specification. The specification expressly defines "intron" as "untranslated DNA sequences between exons, together with 5' and 3' untranslated regions associated with a genetic locus. In addition, the term is used to refer to the spacing

Claim Language (Construed Terms in Bold)	Joint Construction or	
	Plaintiff's Proposed Construction and Evidence in Support	**Defendant's Proposed Construction and Evidence in Support**
	that spans an intron sequence and defines a DNA sequence in genetic linkage with an allele to be detected. The primer-defined DNA sequence contains a sufficient number of intron sequence nucleotides to characterize the allele."); '179 patent col. 4: 6-8 ("The present invention is based on the finding that intron sequences contain genetic variations that are characteristic of adjacent and remote alleles on the same chromosome"); '179 patent col. 8: 32-34 ("...highly conserved intron regions, e.g., promoters, operators and other DNA regulatory regions"); '179 patent, col. 8: 39-41 ("...highly conserved intron sequences (e.g. promoters, enhancers, or other regulatory regions)"); '179 patent col. 43: 48-51 ("...the method can detect genetic diseases that are not associated with coding region variations but are found in regulatory or other untranslated regions of the genetic locus"); '179 patent col. 45: 5-8 ("Furthermore, any mutations which may be associated with noncoding regulatory regions can also be detected by the method and will be identified by the screening process"); '652 application, Preliminary Amendment dated 9/23/92, pg, 4, 2nd paragraph ("Support for substituting the phrase 'non-coding region sequence' for 'intron' is found in the Specification at pg. 10, lines 29-33 which defines the term 'intron'"); '239 application, Amendment dated 6/8/92, pg. 3, 1st paragraph ("Support for substituting the phrase 'non-coding region sequence selected from the group	sequences between genetic loci (intergenic spacing sequences) which are not associated with a coding region and are colloquially referred to as "junk". While the art traditionally uses the term "intron" to refer only to untranslated sequences between exons, this expanded definition was necessitated by the lack of any art recognized term which encompasses all non-exon sequences." Col. 5:40-50.

Claim Language (Construed Terms in Bold)	Joint Construction or	
	Plaintiff's Proposed Construction and Evidence in Support	**Defendant's Proposed Construction and Evidence in Support**
	consisting of untranslated sequences between exons, 5' and 3' untranslated regions associated with a genetic locus, and spacing sequences between genetic loci' for 'intron' in Claims 1 and 7 is found in the Specification at page 10, lines 29-33 which defines the term "intron'")	
said primer pair defining a DNA sequence which is **in genetic linkage** with said genetic locus **in genetic linkage** Found in claim numbers: '179 Patent: 1 and 9	**in genetic linkage** **PROPOSED CONSTRUCTION:** The term "genetic linkage" refers to a tendency of DNA sequences on the same chromosome to be inherited together. DNA sequences in genetic linkage are on the same chromosome and tend to be inherited together. **DICTIONARY/TREATISE DEFINITIONS:** Dictionary of Biochemistry and Molecular Biology (1989) ("**linkage** - any association of genes in inheritance that exceeds that to be expected from the independent assortment and that is due to their being located on the same chromosome; linkage is assessed by the tendency of two markers to remain together during recombination"); Henderson's Dictionary of Biological Terms (1989) ("the tendency for some parental alleles to be inherited together, in opposition to Mendel's law of independent assortment, and which is due to their presence close together on the same chromosome"); Recombinant DNA, 2nd Edition (1992), pg. 519 ("Coinheritance, or genetic linkage, of disease gene and	**in genetic linkage** **PROPOSED CONSTRUCTION:** genetic linkage: the term "genetic linkage" means the degree to which DNA sequences are inherited together. The term cannot be construed in the context of the claim without reference to the preceding word "in." DNA sequences in genetic linkage are on the same chromosome and are inherited together. **INTRINSIC EVIDENCE:** The claims must be read in view of the specification, of which they are a part. The specification contains express definitions of terms and thus acts as a dictionary. The specification expressly defines "linkage." "The term 'linkage', as used herein, refers to the degree to which regions of genomic DNA are inherited together. Regions on different chromosomes do not exhibit linkage and are inherited together 50% of the time. Adjacent genes that are always inherited together exhibit 100% linkage." Col. 5:21-25. The specification also provides support. "When the amplified DNA sequence does not include all or a

Claim Language (Construed Terms in Bold)	Joint Construction or	
	Plaintiff's Proposed Construction and Evidence in Support	**Defendant's Proposed Construction and Evidence in Support**
	marker suggests that they are physically close together on the chromosome. Linkage is a familiar concept in genetics and dates back to the early studies on *Drosophila*, when it was shown that combinations of genes tended to be inherited as groups, linked together because they are close to each other on the same chromosome."); Genes IV (1990) ("**Linkage** describes the tendency of genes to be inherited together as a result of their location on the same chromosome; measured by percent recombination between loci") **INTRINSIC EVIDENCE:** '179 patent, col. 5: 20-24 ("The term 'linkage', as used herein, refers to the degree to which regions of genomic DNA are inherited together. Regions on different chromosomes do not exhibit linkage and are inherited together 50% of the time. Adjacent genes that are always inherited together exhibit 100% linkage"); '179 patent, col. 5: 32-38 ("As used herein, 'haplotype' is a region of genomic DNA on a chromosome which is bounded by recombination sites such that genetic loci within a haplotypic region are usually inherited as a unit. However, occasionally, genetic rearrangements may occur within a haplotype. Thus, the term haplotype is an operational term that refers to the occurrence on a chromosome of linked loci."); '179 patent, col. 8: 52-54 ("The amplified DNA sequence is located in a region of genomic DNA that contains genetic variation which is in genetic linkage with the allele to be	portion of an intron adjacent to the variable exon(s), the sequence must also satisfy a second requirement. The amplified sequence must be sufficiently close to the variable exon(s) to exclude recombination and loss of linkage disequilibrium between the amplified sequence and the variable exon(s)." Col 9:19-25. During prosecution, patentee argued that "DNA sequences which are in genetic linkage are regions of genomic DNA that are inherited together" and points to the definition of linkage in the specification. Amendment, May 6, 1991, p.5.

Claim Language (Construed Terms in Bold)	Joint Construction or	
	Plaintiff's Proposed Construction and Evidence in Support	**Defendant's Proposed Construction and Evidence in Support**
	detected. Preferably, the sequence is located in an intron sequence adjacent to an exon of the genetic locus. More preferably, the amplified sequence includes an intervening sequence adjacent to an exon that encodes the allelic variability associated with the locus (a variable exon)"); '179 patent col. 8: 65 to col. 9: 3 (Alternatively, the amplified sequence can be in an intron which does not border an exon of the genetic locus. Such introns are located in the downstream or upstream gene flanking regions or even in an intervening sequence in another genetic locus which is in linkage disequilibrium with the allele to be detected"); '179 patent, col. 9: 21-25 ("The amplified sequence must be sufficiently close to the variable exon(s) to exclude recombination and loss of linkage disequilibrium between the amplified sequence and the variable exon(s)"); '179 patent, col. 9: 28-29 ("The amplified sequence can be outside of the genetic locus but is preferably within the genetic locus"); '239 application, amendment dated 5/6/91, pg. 5, ("The term 'genetic linkage' in Claims 1 and 7 is clear. In particular, it is well understood by those of skill in the art that DNA sequences which are in genetic linkage are regions of genomic DNA that are inherited together. Additionally, the term is defined in the specification at page 10, lines 8-13")	

Claim Language (Construed Terms in Bold)	Joint Construction or Plaintiff's Proposed Construction and Evidence in Support	Defendant's Proposed Construction and Evidence in Support
and contains a sufficient number of non-coding region sequence nucleotides to produce an amplified DNA sequence **characteristic of said allele**; and **characteristic of** [...] **allele[s]** Found in claim numbers: '179 Patent: 1, 4, 5, 9, 26. 27, 28, 29, and 33	**characteristic of [...] allele[s]** **PROPOSED CONSTRUCTION:** capable of distinguishing at least one allele from at least one other allele. More than one amplified DNA sequence may be used for loci where alleles differ by single nucleotide substitutions that are not unique to the allele or when information regarding remote alleles (haplotypes) is desired **DICTIONARY/TREATISE DEFINITIONS:** Dorland's Medical Dictionary (1988) "typical of an individual or other entity"); Longman Illustrated Science Dictionary (1981) ("any part, shape, way of behaving, by which an organism, or group of organisms, can be recognized, *e.g.* (a) hair on the body is a characteristic of mammals; (b) feathers are a characteristic of birds, (c) green-coloured leaves are a characteristic of most plants; (d) walking on two legs is a characteristic of man"); Stedman's Medical Dictionary (1995) ("typical or distinctive of a particular disorder") **INTRINSIC EVIDENCE:** '179 patent Abstract ("The present invention provides a method for detection of at least one allele of a genetic locus"); '179 Patent, col. 3: 67 to col. 4: 5 ("The amplified DNA sequence is analyzed to detect the presence of a genetic variation in the amplified DNA sequence such as a change in the length of the sequence, gain or loss of a restriction site or	**characteristic of [...] allele[s]** **PROPOSED CONSTRUCTION:** characteristic: the term "characteristic" means a trait, quality or property that is unique to the allele. **INTRINSIC EVIDENCE:** characteristic: Patentee uses the term in the specification as follows: "[A]nalytical methods to unambiguously characterize the alleles of the genetic loci associated with the complex have been sought." Col. 2:8-11. "The length of the amplified sequence which is required to include sufficient genetic variability to enable discrimination between all alleles of a locus bears a direct relation to the extent of the polymorphism of the locus (the number of alleles). That is, as the number of alleles of the tested locus increases, the size of an amplified sequence which contains sufficient genetic variations to identify each allele increases." Col. 7:34-41. "One of ordinary skill can readily determine whether an endonuclease produces RFLP fragments having distinctive fragment lengths.... Distinguishable patterns will be readily recognized by determining whether comparison of two or more digest patterns is sufficient to demonstrate characteristic differences between the patterns of the alleles." Col. 17:6-15.

Claim Language (Construed Terms in Bold)	Joint Construction or Plaintiff's Proposed Construction and Evidence in Support	Defendant's Proposed Construction and Evidence in Support
	substitution of a nucleotide. The variation is characteristic of the allele to be detected") '179 Patent, col. 4: 6-8 ("The present invention is based on the finding that intron sequences contain genetic variations that are characteristic of adjacent and remote alleles on the same chromosome"); '179 patent, col. 7: 24-28 ("The amplified DNA sequence that is defined by the primers contains a sufficient number of intron sequence nucleotides to distinguish between at least two alleles of an adjacent locus, and preferably, to identify the allele of the locus which is present in the sample"); '179 patent, col. 10, line 66 to col. 11, line 4 ("When the variation to be detected is a change in a restriction site, the amplified DNA sequence necessarily contains at least one restriction site which (1) is present in one allele and not in another, (2) is apparently located in a different position in the sequence of at least two alleles, or (3) combinations thereof"); '179 patent, col. 11: 12-17 ("In a most preferred embodiment, the sequence contains a region detectable by a probe that is present in only one allele of the genetic locus. However, combinations of probes which react with some alleles and not others can be used to characterize the alleles"); '179 patent, col. 11: 18-24 ("For the method described herein, it is contemplated that use of more than one amplified DNA sequence and/or use of more than one analytical method per amplified DNA sequence may be required for highly polymorphic loci, particularly for	"The presence of an amplified sequence indicates the presence of the allele, which is confirmed by production of characteristic RFLP patterns." Col. 39:48-50. "To analyze RFLP patterns, fragments in the digest are separated by size and then visualized. In the case of typing for a particular HLA locus, the analysis is directed to detecting the two DNA allele sequences that uniquely characterize that locus in each individual." Col. 39:51-54. "As shown in the Table, each of the endonucleases produces a characteristic RFLP fragment pattern which can readily distinguish which of the three A alleles is present in a sample." Col. 42:15-19. "A genetic screening program (based on amplification of exon regions and analysis of the resultant amplified DNA sequence with probes specific for each of the mutations or with enzymes producing RFLP patterns characteristic of each mutation) may take years to develop. Such tests would depend on detection and characterization of each of the mutations...." Col. 44:55-62. Further, patentee argued that "characteristic" is defined in Webster's Dictionary as "a trait, quality or property or a group of them distinguishing an individual, group or type," and that as an example, "characteristic of' would be "DNA sequences which are present

Claim Language (Construed Terms in Bold)	Joint Construction or	
	Plaintiff's Proposed Construction and Evidence in Support	**Defendant's Proposed Construction and Evidence in Support**
	loci where alleles differ by single nucleotide substitutions that are not unique to the allele or when information regarding remote alleles (haplotypes) is desired."); '179 patent col. 43: 43-48 ("Carriers of genetic diseases and those affected by the disease can be identified by use of the present method. Depending on the disease, the screening analysis can be used to detect the presence of one or more alleles associated with the disease or the presence of haplotypes associated with the disease"); '179 patent Claim 5 ("The method of claim 1 wherein said amplified DNA sequence is characteristic of at least one adjacent allele and at least one nonadjacent allele"); '239 application, amendment dated 5/6/91, pg. 5, ("The meaning of the phrase 'characteristic of' in Claims 1, 4 and 5 is clear on its face and would be readily understood by those of ordinary skill in the art. As shown in Exhibit 1 attached hereto, Webster's Dictionary defines the term 'characteristic' as 'a trait, quality or property or a group of them distinguishing an individual, group or type'. That definition is consistent with the use of the phrase in the claims. For example, in Claim 1, the amplified DNA sequence is said to be 'characteristic of said allele.' There are numerous examples throughout the specification of amplified sequences that are characteristic of an allele to be detected. Specifically, those sequences are DNA sequences which are present in only one allele of the genetic locus"); '239	in only one allele of the genetic locus." Amendment, May 6, 1991, p. 5 (emphasis added) "The prior art recognized that occasionally a sequence polymorphism in intron was empirically determined to correlate with a particular allele of a genetic locus...[t]o further distinguish the claimed method from the prior correlation of particular, empirically-determined allele-associated polymorphisms in introns, the claims have been limited to the analysis of multi-allelic genetic loci." Amendment, May 6, 1991, p.8. "In any event, the article describes one more empirically-determined sequence polymorphism in an intron that correlates with one allele of a bi-allelic genetic loci." Amendment, May 6, 1991, p.10 (emphasis added). "Mullis does not suggest that intron sequences are generally informative and can be used to identify alleles of multi-allelic loci." Amendment, May 6, 1991, p.12. "Classical cDNA RFLP analysis can identify some alleles and haplotypes associated with a genetic locus. However, the cDNA RFLP patterns often cannot produce distinguishable patterns for all alleles of haplotypes associated with multi-allele loci." Amendment, January 14, 1993, p.9. "The basis of Applicant's invention is that variations (polymorphisms) in

Claim Language (Construed Terms in Bold)	Joint Construction or	
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	application. Amendment dated 4/14/92, pp. 16-17 ("The exon/intron junction is a highly conserved portion of all interrupted genes since the region contains signals which are crucial for splicing of mammalian pre-mRNA. Accompanying this amendment is a copy of pages 639-640 of Molecular Biology of the Gene. Those pages detail that in mammalian genes like the phenylketonuria gene the sequences at the exon/intron boundaries are highly conserved. Therefore such sequences do not contain polymorphism that are indicative of the coding region alleles. The sequences therefore do not fall within the terms of the claims")	the non-coding regions are also indicative of the coding region allele. However, since there are so many more non-coding region nucleotides. Applicant was able to identify polymorphisms indicative of a single allele of the locus. That is, Applicant was able to identify unique polymorphisms or unique polymorphic patterns for each allele." Amendment, September 24, 1993, p.19 (emphasis added).
b) **analyzing the amplified DNA sequence** to detect the allele. **analyzing [the/said] amplified DNA sequence** Found in claim numbers: '179 Patent: 1 and 9	**analyzing [the/said] amplified DNA sequence** **JOINT CONSTRUCTION:** studying the genetic variation within at least the non-coding region of the amplified DNA sequence	
b) analyzing the amplified DNA sequence **to detect the allele.** **to detect the allele** Found in claim numbers: '179 Patent: 1 and 9	**to detect the allele** **JOINT CONSTRUCTION:** to determine the existence, presence, or fact of the allele	
2. The method of claim 1		
wherein said amplified DNA sequence includes at least about 300 nucleotides **corresponding to** non-	**correspond[ing/s] to non-coding region sequences** **JOINT CONSTRUCTION:** that are non-coding region	

Claim Language (Construed Terms in Bold)	Joint Construction or	
	Plaintiff's Proposed Construction and Evidence in Support	Defendant's Proposed Construction and Evidence in Support
coding region sequences. **correspond[ing/s] to non-coding region sequences** Found in claim numbers: '179 Patent: 2, 6, and 17	sequences	
3. The method of claim 1		
wherein said non-coding region sequence is **adjacent** to an exon encoding said allele. **adjacent** Found in claim numbers: '179 Patent: 3, 5, and 29	**adjacent** **JOINT CONSTRUCTION:** immediately preceding or following	
4. The method of claim 1		
wherein said amplified DNA sequence is characteristic of at least one **nonadjacent** allele. **nonadjacent** Found in claim numbers: '179 Patent: 4 and 5	**nonadjacent** **JOINT CONSTRUCTION:** not adjacent	
9. A method for detection of at least one allele of a multi-allelic genetic locus comprising:		
a) amplifying genomic DNA with a primer pair that spans a non-coding region sequence,		
said primer pair defining a DNA sequence which is in genetic linkage with said allele		

Claim Language (Construed Terms in Bold)	Joint Construction or Plaintiff's Proposed Construction and Evidence in Support	Defendant's Proposed Construction and Evidence in Support
and contains a sufficient number of non-coding region sequence nucleotides to produce an amplified DNA sequence characteristic of said allele; and		
b) analyzing said amplified DNA sequence **to determine** the presence of a genetic variation in said amplified sequence to detect the allele. **to determine** Found in claim numbers: '179 Patent: 9 and 24	**to determine** **PROPOSED CONSTRUCTION:** to conclude or ascertain **DICTIONARY/TREATISE DEFINITIONS:** The Random House Dictionary of the English Language, 2nd Edition (1987) (**determine, determining** - "to conclude or ascertain as after reasoning, observation, etc."); Genes IV (1990), pg. 94 ("If several sites for one enzyme lie very close together (within 50 bp), very small fragments may be generated that are lost from the agarose gel. Of course, this will result in a discrepancy when the molecular weights of the other fragments are totaled, but this would not necessarily be considered sinister by itself, since there are always modest experimental discrepancies when fragment sizes are compared."); *Id.*, pg. 94-95 ("Locating point mutations on the restriction map is more difficult. Occasionally they may change target sites for restriction enzymes, but otherwise they remain undetectable, since the sizes of the restriction fragments remain the same in wild-type and mutant DNAs. To locate these base substitutions, it may be necessary to determine the sequence of the DNA.")	**to determine** **PROPOSED CONSTRUCTION:** to determine: the term "to determine" has it usual and ordinary meaning, to fix conclusively or authoritatively. **DICTIONARY/TREATISE DEFINITIONS:** to determine: Webster's Ninth New Collegiate Dictionary (1989), p.346 ("determine *vb* la: to fix conclusively or authoritatively, 4: to find out or come to a decision about by investigation, reasoning, or calculation"). **INTRINSIC EVIDENCE:** "The endonuclease cleaves the amplified DNA sequence to yield a set of fragments having distinctive fragment lengths. Usually the amplified sequence is divided, and two or more endonuclease digests are produced. The digests can be used, either separately or combined, to produce RFLP patterns that can distinguish between individuals. Additional digests can be prepared to provide enhanced specificity to distinguish between even closely related individuals with the same HLA type." Col. 39:29-38. "For forensic applications, analysis of the sample DNA of the suspected

Claim Language (Construed Terms in Bold)	Joint Construction or	
	Plaintiff's Proposed Construction and Evidence in Support	**Defendant's Proposed Construction and Evidence in Support**
	INTRINSIC EVIDENCE: '179 patent col. 39: 59-64 ("...the analysis need not involve identifying a particular locus or loci but can be done by comparing single or multiple RFLP patterns of one individual with that of another individual using the same restriction endonucleases and primers to determine similarities and differences between the patterns"); '179 patent col. 40: 56-59 ("For paternity testing, the analysis involves comparison of DNA of the child, the mother and the putative father to determine the probability that the child inherited the obligate haplotype DNA from the putative father"); '179 patent col. 1: 55-57 ("The problems encountered in attempting to determine the HLA type of an individual are exemplary of problems encountered in characterizing other genetic loci"); '179 patent col. 2: 3-7 ("HLA determinations are used in paternity determinations, transplant compatibility testing, forensics, blood component therapy, anthropological studies, and in disease association correlations to diagnose disease or predict disease susceptibility"); '179 patent col. 2: 14-16 ("Alleles of Class I loci and Class II DR and DQ loci are typically determined by serological methods"); '179 patent col. 4: 16-18 ("In a preferred embodiment, the method is used to determine HLA allele type and haplotype"); '179 patent col. 15: 41-50 ("The presence of a second amplified sequence can be determined by quantitating the amount of DNA at the start and the	perpetrator of the crime and DNA found at the crime scene are analyzed concurrently and compared to determine whether the DNA is from the same individual. The determination preferably includes analysis of at least three digests of amplified DNA of the DQA1 locus and preferably also of the A locus. More preferably, the determination also includes analysis of at least three digests of amplified DNA of an additional locus, e.g. the DPB locus. In this way, the probability that differences between the DNA samples can be discriminated is sufficient." Col.40:45-55. "The DNA of an individual is analyzed to determine which of the three haplotypes of the HLA DQA1 0102 locus are present. Genomic DNA is amplified as described in Example 3. Each of the amplified DNA sequences is sequenced to identify the haplotypes of the individual. The individual is shown to have the haplotypes DR15 DQ6 Dw2; DR13 DQ6 Dw19." Col. 57:25-27.

Claim Language (Construed Terms in Bold)	Joint Construction or	
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	end of the second amplification reaction. Methods for quantitating DNA are well known and include determining the optical density at 260 (OD_{260}), and preferably additionally determining the ratio of the optical density at 260 to the optical density at 280 (OD_{260}/ OD_{280}) to determine the amount of DNA in comparison to protein in the sample"); '179 patent col. 21: 59-61 ("The present method of analysis of genetic variation in an amplified DNA sequence to determine allelic difference in sample DNA can be used to determine HLA type")	
b) analyzing said amplified DNA sequence to determine the presence of a **genetic variation** in said amplified sequence to detect the allele. **genetic variation** Found in claim numbers: '179 Patent: 9	**genetic variation** **JOINT CONSTRUCTION:** any difference in DNA sequence at a given place on a chromosome	
15. The method of claim 9		
wherein said allele is **associated with** a monogenic disease. **associated with** Found in claim numbers: '179 Patent: 15, 35, and 36	**associated with** **JOINT CONSTRUCTION:** closely connected with or related to	
wherein said allele is associated with a **monogenic disease**.	**monogenic disease** **JOINT CONSTRUCTION:** a disease caused by a single gene	

Claim Language (Construed Terms in Bold)	Joint Construction or	
	Plaintiff's Proposed Construction and Evidence in Support	Defendant's Proposed Construction and Evidence in Support
monogenic disease Found in claim numbers: '179 Patent: 15 and 16		

US Patent No. 5,851,762
GENOMIC MAPPING METHOD BY DIRECT HAPLOTYPING USING INTRON SEQUENCE ANALYSIS

Claim Language (Construed Terms in Bold)	Joint Construction or	
	Plaintiff's Proposed Construction and Evidence in Support	**Defendant's Proposed Construction and Evidence in Support**
1. A genomic mapping method for identifying informative, polymorphic markers and using said markers **to identify** a chromosomal region associated with a trait, comprising: **to identify** Found in claim numbers: '762 Patent: 1, 7, and 9	**to identify** GTG asserts that the preamble is not a limitation and therefore this term should not be construed in the preamble. Element (j) of this claim is clear as written and refers to identifying a chromosomal region having a greater degree of haplotype heterogeneity restriction <u>as an indication that the region is associated with the trait</u>. However if the court determines that the preamble is a limitation and requires a construction for the term "to identify" in the preamble, then it should be construed in light of element (j), and GTG offers the following construction: **PROPOSED CONSTRUCTION:** to establish as being a particular [chromosomal region as an indication that the region is associated with the trait] **DICTIONARY/TREATISE DEFINITIONS:** **Identify** *The Random House Dictionary of the English Language*, 2nd Ed. Unabridged, 1987 ("to ... establish as being a particular ... thing."; "(*Biol.*) to determine to what group (a given specimen) belongs.") **INTRINSIC EVIDENCE:** Claim 1(j) ("... **to identify** a	**to identify** Applera contends that the preamble is limiting and that the Court should construe this term as it is used in the preamble. **PROPOSED CONSTRUCTION:** <u>to identify</u>: the term has its usual and ordinary meaning of establishing the identity of **DICTIONARY/TREATISE DEFINITIONS:** <u>identify</u>: Webster's Ninth New Collegiate Dictionary (1989), p. 597 ("2 a: to establish the identity of") **INTRINSIC EVIDENCE:** "The present invention is an improved mapping method which is based on the ability to identify haplotypes of individuals through analysis of non-coding region sequence variation patterns, particularly intron sequence variation patterns. ... By analyzing haplotype restriction associated with a region of interest, one can determine the direction of, and ultimately, the location of a gene of interest. In addition, direct haplotyping facilitates locating a disease-associated gene of interest without the need to resort to linkage analysis based on family studies. Direct analysis of haplotypes of normals and of those affected by the disease can be performed to identify

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	subseries of adjacent selected chromosomal regions having a greater degree of haplotype heterogeneity restriction at a central selected chromosomal region in said subseries than at selected chromosomal regions at the ends of said subseries as an indication that said central selected chromosomal region is associated with the trait.") [emphasis added]	the locus associated with a disease." Col. 7:44-65.
1. A genomic mapping method for identifying informative, polymorphic markers and using said markers to identify a chromosomal region **associated with** a trait, comprising: **associated with** Found in claim numbers: '762 Patent: 1 and 9	**associated with** **JOINT CONSTRUCTION:** closely connected with or related to	
1. A genomic mapping method for identifying informative, polymorphic markers and using said markers to identify a chromosomal region associated with **a trait**, comprising: **a trait, the trait** Found in claim numbers: '762 Patent: 1, 9, 10, and 11	**a trait, the trait** **JOINT CONSTRUCTION:** an inherited characteristic	
(a) obtaining a first set of genomic DNA samples from a plurality of individuals representing		

Claim Language (Construed Terms in Bold)	Joint Construction or	
	Plaintiff's Proposed Construction and Evidence in Support	**Defendant's Proposed Construction and Evidence in Support**
the diversity of a general population;		
(b) amplifying a **non-coding sequence** from a selected chromosomal region in each of said first set of genomic DNA samples to produce a first set of amplified DNA sequences; **non-coding sequence[s]** Found in claim numbers: '762 Patent: 1, 5, 8, and 9	**non-coding sequence** **PROPOSED CONSTRUCTION:** any untranslated DNA sequences, such as sequences between exons, the 5' and 3' untranslated regions, and sequences between genetic loci **DICTIONARY/TREATISE DEFINITIONS:** *Webster's Medical Desk Dictionary*, Merriam-Webster, 1986 (noncoding sequence is defined as "Not specifying the genetic code.") **INTRINSIC EVIDENCE:** P. 10 of the A & R dated 21-Dec-93 of the Parent Application No.: 07/971,856 ("...non-coding sequence nucleotides are nucleotides that do not code for amino acids ... non-coding sequences comprise introns, 5' and 3' untranslated regions, promotors and intergenic sequences. In short, non-coding regions sequences are any sequences which do not code for a protein.") Col. 7, lines 16-19 ("The present invention is based on the finding that non-coding region sequences, particularly intron sequences, contain genetic variations that are characteristic of alleles of adjacent and remote, linked genetic loci on the chromosome"); Col. 11, lines 28-35 ("A similar or greater level of variability is found in intergenic regions because less selective pressure is maintained in these regions than for active genes. Therefore those sequences can also be used for the location of the	**non-coding sequence** **PROPOSED CONSTRUCTION:** non-coding sequence: all non-exon sequences, including sequences between exons, the 5' and 3' untranslated regions, and sequences between genetic loci **INTRINSIC EVIDENCE:** non-coding sequence: The specification states "non-coding sequences in any region for which there is about 200 to 500 nt of sequence information, particularly at a genetic locus, can be rapidly amplified and analyzed, and thus provide a marker which can be economically screened." Col. 8:1-5. "More specifically, using the methods and reagents of this invention, two types of non-coding sequence variation associated with genetic loci and intergenic sequences have been found." Col. 11:33-36. Further, the patentee during prosecution argued that it is clear that non-coding sequences comprise introns, 5' and 3' untranslated regions, promoters, and intergenic sequences. In short, non-coding regions sequences are any sequences which do not code for a protein." Amendment, December 21, 1993, p.10. In distinguishing a reference, the patentee also argued that "the amplified DNA sequence of the claimed method coprises a genetic

Claim Language (Construed Terms in Bold)	Joint Construction or	
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	markers of this invention. More specifically, using the methods and reagents of this invention, two types of non-coding sequence variation associated with genetic loci and intergenic sequences have been found")	variation found in non-coding sequences, not a polymorphism in exon sequences....Knowing that polymorphisms in exon sequences are useful in HLA DP typing does not teach or suggest that non-coding sequences contain genetic variations that are characteristic of alleles or haplotypes at adjacent or remote genetic loci." Amendment, July 18, 1995, p. 14-15.
(c) analyzing said first set of amplified DNA sequences **to determine** whether said non-coding sequence comprises a plurality of polymorphic regions, **to determine** Found in claim numbers: '762 Patent: 1	**to determine** **PROPOSED CONSTRUCTION:** to conclude or ascertain **DICTIONARY/TREATISE DEFINITIONS:** The Random House Dictionary of the English Language, 2nd Edition (1987)-(**determine, determining -** "to conclude or ascertain as after reasoning, observation, etc.") **INTRINSIC EVIDENCE:** Col. 3, lines 48-50 ("It is noted that a positional cloning project should not be initiated unless the clinical status of each family member can be determined with a high degree of certainty."); Col. 7, lines 31-35 ("The mapping method provides information about the degree of polymorphism of a genetic locus by determining the number of allelic and sub-allelic (haplotypic) patterns produced for the locus by analyzing the DNA of numerous individuals"); Col. 7, lines 58-60 ("By analyzing haplotype restriction associated with a region of interest, one can determine the direction of and, ultimately, the location of a gene of interest."); Col. 14, lines 20-22 ("By	**to determine** **PROPOSED CONSTRUCTION:** to determine: the term "to determine" has its usual and ordinary meaning and thus means to fix conclusively or authoritatively. **DICTIONARY/TREATISE DEFINITIONS:** determine: Webster's Ninth New Collegiate Dictionary (1989), p. 346 ("1 a: to fix conclusively or authoritatively").

Claim Language (Construed Terms in Bold)	Joint Construction or	
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	analyzing DNA from numerous individuals, the number of alleles and of haplotypes associated with a region of interest can be determined");Col. 16, lines 16-19 ("Once a primer pair or primer pair/endonuclease combination is selected, the DNA of about 100 individuals would be amplified and the lengths of the sequences (fragments) would be determined ");Col. 28, lines 29-32 ("In that case, each of the resultant amplified DNA sequences is of a distinguishable length and is electrophoresed to determine the group of alleles present in the sample"); Col. 30, lines 21-23 ("One of ordinary skill can readily determine whether an endonuclease produces RFLP fragments having distinctive fragment lengths")	
(c) analyzing said first set of amplified DNA sequences to determine whether said non-coding sequence comprises a **plurality of polymorphic regions,** **plurality of polymorphic regions** Found in claim numbers: '762 Patent: 1, 9, and 16	**plurality of polymorphic regions** **JOINT CONSTRUCTION:** more than one polymorphic region	
(c) analyzing said first set of amplified DNA sequences to determine whether said non-coding sequence comprises a plurality of **polymorphic regions,**	**polymorphic region** **JOINT CONSTRUCTION:** a region of genomic DNA having one or more polymorphic sites	

Claim Language (Construed Terms in Bold)	Joint Construction or	
	Plaintiff's Proposed Construction and Evidence in Support	**Defendant's Proposed Construction and Evidence in Support**
polymorphic regions Found in claim numbers: '762 Patent: 1, 16, 22, and 23		
wherein said plurality of polymorphic regions **defines** a plurality of haplotypic patterns detectable by a selected technique for analyzing genetic variation; **defines** Found in claim numbers: '762 Patent: 1 and 9	**defines** **JOINT CONSTRUCTION:** fixes or marks the limits of	
wherein said plurality of polymorphic regions defines a plurality of **haplotypic patterns** detectable by a selected technique for analyzing genetic variation; **haplotypic pattern[s]** Found in claim numbers: '762 Patent: 1, 9, 18, and 19	**haplotypic pattern** **PROPOSED CONSTRUCTION:** data, from an analytical method, that is characteristic of a particular haplotype **DICTIONARY/TREATISE DEFINITIONS:** **pattern** *The Random House Dictionary of the English Language, 2nd Ed. Unabridged* ("forming a ... characteristic arrangement") **INTRINSIC EVIDENCE:** P. 9 of the A & R dated 21-Dec-1993 of the Parent Application No.: 07/971,856 ("a genetic variation can be identified by a variety of techniques that detect such differences in sequences between different individuals... [Method comprises] identifying a genetic variation by any of the available	**haplotypic pattern** **PROPOSED CONSTRUCTION:** haplotypic pattern: a "haplotypic pattern" is a pattern of DNA fragments that have been separated according to mobility and visualized, and which is uniquely indicative of the presence of a particular haplotype. **INTRINSIC EVIDENCE:** "The present invention is an improved genomic mapping method which is able to generate highly informative polymorphic sites throughout the genome. In addition to being highly polymorphic, the sites can be used to generate patterns that identify allelic and sub-allelic haplotypes associated with the region." Abstract. The specification describes the term "pattern." "In particular, primer-

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	techniques."); Col. 7, lines 31-35 ("The mapping method provides information about the degree of polymorphism of a genetic locus by determining the number of allelic and sub-allelic (haplotypic) patterns produced for the locus by analyzing the DNA of numerous individuals"); Col. 17, lines 29-35 ("A detailed description of selection of primers, amplification methods, and analysis of DNA sequences is provided below. Those techniques can be used initially to determine the patterns produced by common alleles/haplotypes associated with the locus. Once the common patterns are established, the patterns can be refined so that additional haplotypes associated with a locus can be distinguished."); Col. 17, lines 49-57 ("There are three major types of genetic variations that can be detected within an amplified DNA sequence and used to identify allelic and sub-allelic groups. Those variations, in order of ease of detection, are (1) a change in the length of the sequence, (2) a change in the presence or location of at least one restriction site and (3) the substitution of one or a few nucleotides that does not result in a change in a restriction site. Other variations within the amplified DNA sequence are also detectable"); Col. 17, line 64 to Col. 18, line 47 ("There are four types of techniques which can be used to detect the variations. The first is sequencing the amplified DNA sequence ... The second analytical method uses allele-specific oligonucleotides or sequence-specific oligonucleotides	defined, amplified DNA sequences that include a sufficient number of intron sequence nucleotides can be used to produce patterns which are characteristic of alleles and haplotypes associated with a genetic region of interest. The patterns can be produced by gel electrophoresis length differences in amplified DNA sequences or can be RFLP fragment patterns produced by digestion of the amplified DNA sequences with one or more endonucleases." Col. 7:20-27. Further, "[t]hese non-coding sequence variation patterns can be generated anywhere there is about 200 to 500 bp of sequence information." Col. 11:57-59. "[T]he patterns are readily produced and analyzed for rapid screening. In addition, the patterns are highly informative so that the screening provides much more information than classical RFLP sites. This combination makes intron variation patterns ideal markers for expeditious mapping of disease-associated gene loci." Col. 12:11-16. "Specifically, amplified intron sequences can generate a physical and genetic map that is more dense and more informative for genome searches than prior art maps using less informative markers. The intron- containing, amplified DNA sequences of this invention from unique gene regions provide easily screened and very informative markers that directly provide allele and haplotype information about the

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	probes (ASO or SSO probes) ... A third type of analytical method detects sequences of different lengths ... A fourth and most preferred type of analytical method is based on allele/haplotype-specific amplification to detect the presence of the selected allele/haplotype ... the analytical techniques used to recognize allele-associated genetic variations in the amplified DNA sequence can include use of probes or sequencing of the amplified DNA sequence ... sequencing or use of probes may be the preferred analytical method for some genetic regions."); Office Action dated March 21, 1994, pg. 6 ("several identification techniques, techniques to identify intron sequences[,] techniques for amplification, techniques for mapping, techniques for identifying a variation in said amplified DNA sequences...are known in the art...."); Communication from the USPTO dated July 18, 1996 ("directed to an invention that is **independent or distinct** from the invention originally claimed.") [emphasis added]: *Id.*, ("patentably distinct methods [from the original claims and] involve different starting points...**have different method steps**, and different ultimate goals....") [emphasis added]	locus. In addition to being easily screened and highly informative, the intron variation patterns can be generated and scored faster and less expensively than classical RFLP patterns. This is of particular value in providing the most information in the shortest time for the least cost." Col. 12:24-36. "In addition to identifying sequence polymorphism patterns in a gene, any other region for which there are at least 200, preferably at least 500 bp of sequence information can also be used as a marker site to produce amplified DNA sequences that produce patterns that identify alleles/haplotypes associated with the region." Col. 12:54-59. Further, "[t]he non-coding polymorphic variation patterns of this invention are at least as effective as screening for CA and GA repeats throughout the genome at STS sites in terms of the limited cost and time required for screening in comparison to classical RFLP analyses." Col. 12:61-66. "The next region to be analyzed is preferably sufficiently close to provide some haplotypic patterns characterized by PDLP or RFLP patterns which are shared with the previous locus." Col. 13:11-14. "PDLP and RFLP patterns produced in the analyses are more numerous and more closely linked to the genetic locus than RFLP sites located by classical methods, since the present method can effectively

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		utilize all of the RFLP sites in the amplified DNA sequences." Col. 14:24-28. "Once a primer pair/endonuclease combination is selected, the DNA of about 100 individuals would be amplified and the lengths of the sequences (fragments) would be determined. The lengths of the sequences will fall into patterns related to the alleles(s)/ haplotype(s) of the individuals for that amplified sequence." Col. 16:16-21. "Rather than attempting to determine each defect in a coding region that causes the disease, the present method amplifies intron sequences associated with the locus to identify allelic and sub-allelic patterns. New PDLP and RFLP patterns produced by intron sequences indicate the presence of a previously unrecognized haplotype." Col. 17:23-28. "[T]he fragments for one allele/haplotype of a locus differ in size from the fragments for other alleles/haplotypes of the locus. The patterns produced by separation and visualization of the fragments of a plurality of digests are sufficient to distinguish allelic and sub-allelic patterns for the locus." Col. 29:56-60. The patentee also sought during prosecution to limit the method so as to require the separation of fragments by mobility and visualization. "The inventive method is based on Dr. Simons' discovery

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		that intron sequences contain genetic variations that are characteristic of alleles of adjacent and remote linked genetic loci on a chromosome. In particular, primer-defined, amplified DNA sequences that include a sufficient number of intron sequence nucleotides can be used to produce patterns which are characteristic of alleles and haplotypes associated with a genetic region of interest. The patterns can be produced by length differences in the amplified DNA sequences or can be RFLP fragment patterns produced by digestion of the amplified DNA sequences with one or more endonucleases. Amendment, May 6, 1991, p. 2. "Once the haplotypes for a locus are determined, the haplotypes for a distant region (about 0.01 to 2 million basepairs (Mbp) away) from the first locus are then analyzed in the same manner. The next region to be analyzed is preferably sufficiently close to provide some haplotypic patterns which are shared with the previous locus. That is, some of the PDLPs or RFLP patterns will be identical for alleles of adjacent loci." Pat. Appl. No. 07/550,939, Filed July 11, 1990, Specification, p.13-14. "The present invention is based on Dr. Simons' discovery that variations in the introns correlate with the alleles present at adjacent and remote loci...in contrast to the teachings of the prior art, intron sequences did not vary randomly and that there were variations in the

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		introns that were characteristic of the adjacent allele (the genetic locus in which the intron is located)." Amendment, May 6, 1991, p.6 (emphasis added). "The inventive method is based on Applicant's discovery that intron sequences contain genetic variations that are characteristic of alleles of adjacent and remote linked genetic loci on a chromosome." Amendment, September 26, 1991, p.4-5. The language of the claim indicates that "haplotypic pattern" is "a marker for a haplotype of said selected chromosomal region." Col. 37:62-63. The specification also supports the proposed construction. "Analysis of the patterns of intron variation for a particular group of individuals can identify both the alleles and subtypic or sub-allelic groups (haplotypes) at that locus present in members of the group. By analyzing a groups of individuals representing the greatest ethnic diversity among humans and greatest breed and species variety in plants and animals, patterns characteristic of the most common alleles/haplotypes of the locus can be identified. Additional allelic and haplotypic patterns can be identified by screening larger populations. In this way the degree of polymorphism in alleles/haplotypes associated with any locus of interest can be determined without the need to perform repetitive sequencing of numerous individuals." Col. 13:22-

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		34. It further states that "analysis of haplotypic patterns of patients with a disease, particularly a monogenic disease, produces patterns characteristic of the alleles/haplotypes of those patients at any locus." Col. 13:38-42. Further, "individuals with relatively rare haplotypes, such as those associated with a rare genetic disease, can be recognized by direct evaluation of haplotypic patterns in individuals with the disease." Col. 14:50-53. "Pattern" and "haplotype pattern" were also treated as synonymous by the patentee during prosecution. "By analyzing a groups [sic] of individuals representing the greatest ethnic diversity among humans and greatest breed and species variety in plants and animals, [haplotypic] patterns characteristic of the most common alleles/haplotypes of... [a] locus can be identified. Additional allelic and haplotypic patterns can be identified by screening larger populations. In this way the degree of polymorphism in alleles/haplotypes can be determined without the need to perform repetitive sequencing of numerous individuals. (Page 24 lines 22-35, emphasis added)" Amendment, August 27, 1997, p. 15 (emphases and text brackets in original). "What is claimed is: 1. A method for identifying highly informative, polymorphic markers for genomic mapping comprising: a. identifying a genetic locus on a chromosome; b. identifying at least

Claim Language (Construed Terms in Bold)	Joint Construction or	
	Plaintiff's Proposed Construction and Evidence in Support	**Defendant's Proposed Construction and Evidence in Support**
		one intron sequence within the genetic locus; and c. using an amplified DNA sequence corresponding to the intron sequence as a marker for genomic mapping... 6. A method for identifying highly informative, polymorphic markers for genomic mapping of a region of interest of about 1 megabase comprising; a. identifying cDNA sequences from the region of interest; b. mapping the identified cDNA sequences to a location within the region of interest; and c. identifying the location of at least one intron sequence within the genetic locus associated with the cDNA sequence... 10. A genomic mapping method for analyzing highly polymorphic markers that identify allelic and sub-allelic groups for a genetic locus and one or more adjacent loci comprising; a. amplifying genomic DNA in said genetic locus to produce an amplified DNA sequence which includes a sufficient number of non-coding sequence nucleotides to include a genetic variation that differentiates between at least two alleles or haplotypes of said locus; and b. identifying a variation in said amplified DNA sequence that is characteristic of said allele or haplotype." Patent Application No. 07/971,856, specification, p.68-69, claims 1, 6, and 10. "It is not clear what variation is identified or how this identification is accomplished. Applicant argues that variation means 'changes in

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		length, presence or location of a restriction size' as recited in the specification. This argument is not persuasive. These limitations are not in the claims. The specification can be relied on for guidance but not as a substitute for claim limitations. ... These claims, which recite the names of methods and not specific active method steps, read broadly on all methods that go by these names...The specification lacks any guidance as to how to generalize this protocol...it is not clear how one would select other primers for use with different genes....it would require the undue experimentation of working out additional protocols in order to enable a reasonable number of embodiments of these claims." Office Action, March 21, 1994, p.3-5. "In view of the large breadth the claims embrace and of the instant limited disclosure, the disclosure in the instant specification is not sufficient to satisfy the requirement of 35 U.S.C. §112, first paragraph." Office Action, September 27, 1993, p.4. "There are a variety of techniques which can identify genetic loci...one skilled in the art knows that claim 1 comprises the step of identifying an intron by any of a number of techniques." Amendment, December 21, 1993, p.5-6. "[T]he specification fully describes how to perform the methods of Claim 1....Applicant's general description of the claimed methods is as broad as the claims." Amendment, December 21, 1993, p.13, 16. "Further, the skilled artisan understands that a genetic variation

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		can be identified by a variety of techniques that detect differences in DNA sequences between different individuals. Conventional techniques include restriction fragment polymorphism analysis, hybridization analysis, and direct DNA sequencing." Amendment, June 20, 1994, p.5-6. "Claim 1: A method for identifying informative, polymorphic markers for genomic mapping comprising...e)analyzing said amplified DNA sequence to identify a polymorphism in said amplified DNA sequence, said polymorphism indicative of an allele or haplotype corresponding to said transcribed region, wherein said allele or haplotype differs from other alleles or haplotypes in said coding sequence [for use as a marker for genomic mapping.]" Amendment, August 19, 1996, p.1-2 (emphasis added). "Suitable analysis methods are described in the specification at least at page 48, line 1 to page 63, line 8, and an exemplary analysis is set forth in Example 1." Amendment, January 2, 1997, p.7-8, 11-12 (Applera also relies on the portion of the prosecution history quoted in this section). Claims 21 and 29 as set forth in the Amendment, January 2, 1997, p.1-2, 4.
wherein said plurality of polymorphic regions defines a plurality of haplotypic patterns	**selected technique** **PROPOSED CONSTRUCTION:** any analytical method chosen to	**selected technique** **PROPOSED CONSTRUCTION:** selected technique: a "selected

Claim Language (Construed Terms in Bold)	Joint Construction or	
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detectable by a **selected technique** for analyzing genetic variation; **selected technique** Found in claim numbers: '762 Patent: 1, 9 and 17	detect haplotypic patterns **INTRINSIC EVIDENCE:** P. 9 of the A & R dated 21-Dec-1993 of the Parent Application No.: 07/971,856 ("a genetic variation can be identified by a variety of techniques that detect such differences in sequences between different individuals... [Method comprises] identifying a genetic variation by any of the available techniques."); Col. 17, lines 29-35 ("A detailed description of selection of primers, amplification methods, and analysis of DNA sequences is provided below. Those techniques can be used initially to determine the patterns produced by common alleles/haplotypes associated with the locus. Once the common patterns are established, the patterns can be refined so that additional haplotypes associated with a locus can be distinguished."); Col. 17, line 64 to Col. 18, line 47 ("There are four types of techniques which can be used to detect the variations. The first is sequencing the amplified DNA sequence ... The second analytical method uses allele-specific oligonucleotides or sequence-specific oligonucleotides probes (ASO or SSO probes) ... A third type of analytical method detects sequences of different lengths ... A fourth and most preferred type of analytical method is based on allele/haplotype-specific amplification to detect the presence of the selected allele/haplotype ... the analytical techniques used to recognize allele-associated genetic variations in the amplified DNA	technique" is a method that produces patterns of DNA fragments that have been separated according to mobility and visualized, meaning RFLP analysis, primer defined length polymorphism and allele- and haplotype- specific amplification analysis. **INTRINSIC EVIDENCE:** selected technique: The language of the claim is a limitation. Thus, a "selected technique" is a method of analyzing genetic variation by which a plurality of haplotypic patterns is detectable. Col. 37:56-58. The specification also provides support. "On the way to the goal of ultimately sequencing the entire human genome, the Human Genome Project will generate considerable mapping data and isolate and map RFLPs sequence tagged sites (STS), and cDNAs (ESTs; expressed sequence tags; M. D. Adams, et al Sci. 252:1651-1656 (1991)). Currently the most common method of identifying polymorphic markers is by restriction enzyme analysis using numerous restriction endonucleases. This process is labor intensive. This invention proposes to generate considerably more informative sites rapidly to expedite genome mapping, to identify unknown disease genes, and to provide information for prenatal diagnosis of at-risk fetuses." Col. 1:29-40. "The method also provides a rapid way to generate polymorphic markers throughout the genome,

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	sequence can include use of probes or sequencing of the amplified DNA sequence ... sequencing or use of probes may be the preferred analytical method for some genetic regions")	particularly in any genetic locus of interest. Not only can the markers be identified and screened more readily than classical RFLP sites, but the markers are much more informative than classical RFLP sites, which are either present or absent at any given location." Col. 7:9-15. Further, "for any particular region of interest, the method provides information regarding the degree of polymorphism associated with the region and identifies those individuals with differing allelic and sub- allelic (haplotypic) sequences, enabling characterization of individual variability throughout a population. For a particular region of interest, such characterization avoids repetitive sequencing of individuals with the same genetic sequence." Col. 7:49-57. "Analysis of the patterns of intron variation for a particular group of individuals can identify both the alleles and subtypic or sub-allelic groups (haplotypes) at that locus present in members of the group. By analyzing a groups of individuals representing the greatest ethnic diversity among humans and greatest breed and species variety in plants and animals, patterns characteristic of the most common alleles/haplotypes of the locus can be identified. Additional allelic and haplotypic patterns can be identified by screening larger populations. In this way the degree of polymorphism in alleles/haplotypes associated with any locus of interest can be determined without the need

Claim Language (Construed Terms in Bold)	Joint Construction or	
	Plaintiff's Proposed Construction and Evidence in Support	**Defendant's Proposed Construction and Evidence in Support**
		to perform repetitive sequencing of numerous individuals." Col. 13:22-34. "Minimum sequencing enables sequence comparisons between genetically disparate individuals. In this way one can identify non-homologous regions and make rational selection of sites for restriction analysis or ASP HSP amplification." Col. 14:33-37. "To effect allele-specific or haplotype-specific amplification, at least one primer in each nested primer pair is selected so that the primer hybridizes to the DNA sequence only when the selected sequence polymorphism is present. In this way, the presence of an amplified DNA sequence indicates that the sequence polymorphism is present in the sample. This is in contrast to most prior art DNA amplification methods wherein primers bind to a conserved region and the resultant amplified DNA sequence is analyzed, usually by use of oligoprobes, for the presence of the polymorphism in the amplified sequence." Col. 26:34-44. "PDLP groups and fragment patterns for each of the DQA1 haplotypes with each of the three endonucleases are illustrated in Table 1." Col. 32:65-67. During prosecution, patentee argued that "the specification describes the amplification procedure (page 42, line 21 - page 47, line 36) and the analysis of the amplified DNA using

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		primer defined length polymorphism and RFLP analysis (page 48, lines 1-21). Thus the specification fully describes how to perform the method of Claim 1." Amendment ('856), December 21, 1993, p.13. "Because Applicant's general description of the claimed methods is as broad as the claims, Applicant submits that the specification fully describes the claimed methods." Id. at 16. Further, patentee amended the claims so as to limit the invention to only those methods that produce patterns of DNA fragments that have been separated according to mobility and visualized. Amendment, January 2, 1997, p. 1-2.
(d) **determining the number of haplotypic patterns** associated with said non-coding sequence that are distinct as measured by said selected technique, wherein each haplotypic pattern is a marker for a haplotype of said selected chromosomal region; **determining** Found in claim numbers: '762 Patent: 1	**determining the number of haplotypic patterns** **JOINT CONSTRUCTION:** counting the number of haplotypic patterns that are distinct as measured by the selected technique	
(d) determining the number of haplotypic patterns associated with said non-coding sequence that are distinct as measured by said selected technique, wherein each	**marker for a haplotype** **PROPOSED CONSTRUCTION:** indicator for a haplotype **DICTIONARY/TREATISE DEFINITIONS:**	**marker for a haplotype** **PROPOSED CONSTRUCTION:** marker for a haplotype: the term "marker for a haplotype" is a haplotypic pattern which uniquely identifies a haplotype.

Claim Language (Construed Terms in Bold)	Joint Construction or Plaintiff's Proposed Construction and Evidence in Support	Defendant's Proposed Construction and Evidence in Support
haplotypic pattern is a **marker for a haplotype** of said selected chromosomal region; **marker for a haplotype** Found in claim numbers: '762 Patent: 1	**marker** *The Random House Dictionary of the English Language*, 2nd Ed. Unabridged, 1987 ("something used as a mark or indication.") **INTRINSIC EVIDENCE:** Col. 2, lines 46-51 ("Ideally ... each search of the genome for linkage to a disease gene would reveal linkage between one informative polymorphic marker and the disease phenotype."); Col. 8, lines 7-9 ("For every genetic locus, analysis of one or a few intron sequence markers can identify the alleles/haplotypes associated with the locus."); Col. 11, lines 28-35 ("A similar or greater level of variability is found in intergenic regions because less selective pressure is maintained in these regions than for active genes. Therefore those sequences can also be used for the location of the markers of this invention"); Col 12, lines 17-21 ("In particular, one of the goals of the genome mapping project is to produce dense, evenly spaced markers throughout the genome. As stated previously, the usefulness of a marker is directly related to the degree of polymorphism of the marker"); Prosecution History of Parent Application Serial No.: 07/971,856, page 14 of Amendment and Response dated 21-Dec-1993 ("Such [polymorphic] markers can indicate the presence of a particular allele or haplotype at a given locus....[the] amplified DNA sequence...includes a sufficient number of non-coding sequence nucleotides to include a genetic variation that differentiates	**DICTIONARY/TREATISE DEFINITIONS:** marker: Dictionary of Biochemistry and Molecular Biology, 2d Ed. (1989), p.288 ("*marker*: 1. A mutable site on a chromosome that is useful for cell identification and for genetic studies; the site of a gene of known function and known location on the chromosome.") **INTRINSIC EVIDENCE:** marker for a haplotype: The language of the claim is a limitation, such that each haplotypic pattern is a marker for a haplotype of said selected chromosomal region." Col. 37:61-63. The specification also provides support. "Specifically, amplified intron sequences can generate a physical and genetic map that is more dense and more informative for genome searches than prior art maps using less informative markers. The intron- containing, amplified DNA sequences of this invention from unique gene regions provide easily screened and very informative markers that directly provide allele and haplotype information about the locus." Col. 12:24-36. Patentee also argued during prosecution that "[m]ore specifically, to be useful in genomic mapping, a marker should correspond to a region of DNA that exhibits sufficient conservation in the population that the region can be identified in any individual. In

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	between at least two alleles or haplotypes...")	addition, the marker should be sufficiently polymorphic to facilitate the localization of a gene of interest through positional cloning or linkage analysis." Amendment, July 18, 1995, p. 6.
(d) determining the number of haplotypic patterns associated with said non-coding sequence that are distinct as measured by said selected technique, wherein each haplotypic pattern is a marker for a **haplotype** of said selected chromosomal region; **haplotype** Found in claim numbers: '762 Patent: 1, 9, and 17	**haplotype** **JOINT CONSTRUCTION:** co-occurrence of DNA sequences at linked loci that is inherited as a unit	
(e) repeating steps (a)-(d) to identify a plurality of non-coding sequences, each having a plurality of associated haplotypic patterns, at a series of selected chromosomal regions;		
(f) obtaining a second set of genomic DNA samples from a plurality of individuals with the trait from said general population, wherein said plurality of individuals with the trait is not derived from a single family;		
(g) amplifying said plurality of non-coding sequences from said		

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series of selected chromosomal regions in each genomic DNA sample in said second set to produce a second set of amplified DNA sequences;		
(h) **detecting** the haplotypic pattern for each amplified DNA sequence in said second set to identify the haplotype of each corresponding selected chromosomal region; **detecting** Found in claim numbers: '762 Patent: 1	**detecting** **JOINT CONSTRUCTION:** discovering or ascertaining the existence, presence, or fact of	
(h) detecting the haplotypic pattern for each amplified DNA sequence in said second set **to identify the haplotype** of each corresponding selected chromosomal region; **to identify the haplotype** Found in claim numbers: '762 Patent: 1, 7, and 9	**to identify the haplotype** **PROPOSED CONSTRUCTION:** to establish as being a particular haplotype **DICTIONARY/TREATISE DEFINITIONS:** **Identify** *The Random House Dictionary of the English Language*, 2nd Ed. Unabridged, 1987 ("to ... establish as being a particular ... thing."; "(*Biol.*) to determine to what group (a given specimen) belongs."); *The American Heritage Dictionary*, 2nd Edition, Houghton Mifflin Company Boston, 1982 ("to ascertain the origin, nature, or definitive characteristics of.") **INTRINSIC EVIDENCE:** '762 Patent, Abstract, ("...the sites	**to identify the haplotype** **PROPOSED CONSTRUCTION:** to identify the haplotype: as used herein, "to identify" has its usual and ordinary meaning of establishing the identity of, and thus "to identify the haplotype" means to establish the identity of a unique haplotype. **DICTIONARY/TREATISE DEFINITIONS:** identify: Webster's Ninth New Collegiate Dictionary (1989), p. 597 ("2 a: to establish the identity of"). **INTRINSIC EVIDENCE:** to identify the haplotype: The language of the claim indicates that identification of a haplotype is accomplished by the detection of a unique haplotypic pattern, which pattern is a marker for said

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	can be used to generate patterns that identify allelic and sub-allelic haplotypes..."); Col. 8, lines 7-11 ("For every genetic locus, analysis of one or a few intron sequence markers can identify the alleles/haplotypes associated with the locus"); Col. 13, lines 15-18 ("By analyzing the haplotypic patterns at a given location, the location of genetic loci and of haplotypic regions can be identified"); Col. 28, lines 64-67 ("Thus the sequence polymorphism present in the target DNA can be readily identified by the determining the length of the amplified DNA sequence."); Col. 29, lines 58-60 ("The patterns produced by separation and visualization of the fragments of a plurality of digests are sufficient to distinguish allelic and sub-allelic patterns for the locus."); P. 3 of the A & R dated 6-May-'91 of the Grand Parent Appl. No. 07/550,939 ("Funke reports that an MspI restriction site in the first intron of the apolipoprotein gene was identified by a size comparison of the MspI fragment with a restriction map of the apolipoprotein A-I gene."); P. 9 of the A & R dated 21-Dec-1993 of the Parent Application No.: 07/971,856 ("a genetic variation can be identified by a variety of techniques that detect such differences in sequences between different individuals... [Method comprises] identifying a genetic variation by any of the available techniques.")	haplotype. Col. 37:59-63; 38:48-51; 39:37-48. The Abstract also provides support for this limitation.

Claim Language (Construed Terms in Bold)	Joint Construction or	
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(i) **determining the degree of restriction in haplotype heterogeneity** at each selected chromosomal region for said second set of amplified DNA sequences by comparing the number of haplotypic patterns identified for each selected chromosomal region for said first set of amplified DNA sequences and said second set of amplified DNA sequences; and **determining the degree of restriction in haplotype heterogeneity** Found in claim numbers: '762 Patent: 1 and 9	**determining the degree of restriction in haplotype heterogeneity** JOINT CONSTRUCTION: ascertaining the decrease in the number of different haplotypes	
(i) determining the degree of restriction in **haplotype heterogeneity** at each selected chromosomal region for said second set of amplified DNA sequences by comparing the number of haplotypic patterns identified for each selected chromosomal region for said first set of amplified DNA sequences and said second set of amplified DNA sequences; and **haplotype heterogeneity** Found in claim numbers:	**haplotype heterogeneity** JOINT CONSTRUCTION: the number of different haplotypes	

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'762 Patent: 1 and 9		
(j) comparing the degree of haplotype heterogeneity restriction across said selected chromosomal regions, to identify a **subseries of adjacent selected chromosomal regions** having a greater degree of haplotype heterogeneity restriction at a central selected chromosomal region in said subseries than at selected chromosomal regions at the ends of said subseries as an indication that said central selected chromosomal region is associated with the trait. **subseries of adjacent selected chromosomal regions** Found in claim numbers: '762 Patent: 1 and 9	**subseries of adjacent selected chromosomal regions** **PROPOSED CONSTRUCTION:** a successive subset of chosen chromosomal regions **DICTIONARY/TREATISE DEFINITIONS:** **Sub-** Webster's 9th New Collegiate Dictionary, 1988 ("subordinate portion of..."; "less than completely...") **Series** *Stedman's Medical Dictionary*, 25th *ed.*, William R. Hensyl, ed. Williams & Wilkins, 1990. ("A succession of similar objects following one another in space or time."); *Dorland's Illustrated Medical Dictionary*, 27th Edition, W.B. Saunders Company, 1988 (series: "A group of succession of objects or substances arranged in regular order or forming a kind of chain."); *Taber's Cyclopedic Medical Dictionary*, 15th Edition, F.A. Davis Company, 1985 ("Arrangement of objects in succession or in order."); *The American Heritage Dictionary*, 2nd Edition, Houghton Mifflin Company Boston, 1982 ("A group of things of the same class coming one after the other in succession..."); *Webster's II, New Collegiate Dictionary*, by Houghton Mifflin Company, 1995. ("A number of things or events of the same kind occurring in a row or following one after the other in succession.")	**subseries of adjacent selected chromosomal regions** **PROPOSED CONSTRUCTION:** a subseries of selected chromosomal regions within the same locus or, for intron DNA sequences not associated with a genetic locus, immediately preceding or following that locus. **DICTIONARY/TREATISE DEFINITIONS:** Webster's Ninth New Collegiate Dictionary (1989), p.56 ("adjacent *adj.* 1c: immediately preceding or following"). **INTRINSIC EVIDENCE:** The claims must be read in view of the specification, of which they are a part. The specification contains express definitions of terms and thus acts as a dictionary. The specification expressly states that "the term "adjacent locus" refers to either (1) the locus in which a DNA sequence is located or (2) the nearest upstream or downstream genetic locus for intron DNA sequences not associated with a genetic locus." Col. 9: 26-29. "Once the haplotypes for a region are determined, the haplotypes for a distant region (about 0.01 to 2 million basepairs [Mbp] away) from the first locus are then analyzd in the same manner. The next region to be analyzed is preferably sufficiently close to provide some haplotypic patterns characterized by PDLP or

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	INTRINSIC EVIDENCE: Col. 13, lines 8-11 ("Once the haplotypes for a region are determined, the haplotypes for a distant region (about 0.01 to 2 million basepairs [Mbp] away) from the first locus are then analyzed in the same manner.")	RFLP patterns which are shared with the previous locus. That is, there will be patterns for some of the same haplotypes at an adjacent locus." Col. 13:8-14. Further, "[b]y evaluating the adjacent region of the chromosome in the same manner, the mapping method determines overlapping haplotypic regions (haplocontigs) in a selected region of a chromosome and can be used to establish the haplotypic regions throughout the genome." Col. 14:13-18. "When genomic DNA sequences are available, primers are located to produce an amplified DNA sequence corresponding to an intervening sequence. If the location of the variable exon(s) for a locus is known, the amplified DNA sequence is preferably located in an intron adjacent to the variable exon. More preferably, the amplified DNA sequence will span the variable exon and include a portion, preferably the majority, most preferably all, of both adjacent introns." Col. 15:35-42.
(j) comparing the degree of haplotype heterogeneity restriction across said selected chromosomal regions, to identify a subseries of adjacent selected chromosomal regions having a greater degree of haplotype heterogeneity restriction at a **central selected chromosomal region** in said subseries than at selected	**central selected chromosomal region** **JOINT CONSTRUCTION:** the region which exhibits the highest restriction in haplotype heterogeneity within the identified subseries	

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chromosomal regions at the ends of said subseries as an indication that said central selected chromosomal region is associated with the trait. **central selected chromosomal region** Found in claim numbers: '762 Patent: 1 and 9		
(j) comparing the degree of haplotype heterogeneity restriction across said selected chromosomal regions, to identify a subseries of adjacent selected chromosomal regions having a greater degree of haplotype heterogeneity restriction at a central selected chromosomal region in said subseries than at selected chromosomal regions at the **ends of said subseries** as an indication that said central selected chromosomal region is associated with the trait. **ends of said subseries** Found in claim numbers: '762 Patent: 1 and 9	**ends of said subseries** **JOINT CONSTRUCTION:** positions at the outer bounds of a subseries of adjacent selected chromosomal regions showing less haplotype heterogeneity restriction relative to a central selected chromosomal region	
(j) comparing the degree of haplotype heterogeneity restriction across said selected chromosomal regions, to	**indication** **PROPOSED CONSTRUCTION:** suggestion or sign of	**indication** **PROPOSED CONSTRUCTION:** indication: an "indication" means positive identification of said central

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identify a subseries of adjacent selected chromosomal regions having a greater degree of haplotype heterogeneity restriction at a central selected chromosomal region in said subseries than at selected chromosomal regions at the ends of said subseries as an **indication** that said central selected chromosomal region is associated with the trait. **indication** Found in claim numbers: '762 Patent: 1 and 9	**DICTIONARY/TREATISE DEFINITIONS:** **indication** Webster's 9th New Collegiate Dictionary, 1988 ("something that serves to indicate") **indicate** Webster's 9th New Collegiate Dictionary, 1988 ("sign of...") **INTRINSIC EVIDENCE:** Col. 15, lines 46-54 ("If the amplified sequence contains about 200nt, the location of the first primer is moved about 200 nt to one side of the second primer location and the amplification is repeated until either (1) an amplified DNA sequence that is larger than expected is produced or (2) no amplified DNA sequence is produced, indicating the presence of an intervening sequence that is too large for the amplification method. In either case, the location of an intron sequence has been determined."); Col. 16, lines 66-67 ("Additional data indicate that several other mutations may cause the disease."); Col. 17, lines 1-4 ("Studies of haplotypes of parents of CF patients ... indicated that there are at least 178 haplotypes associated with the CF locus."); Col. 17, lines 26-28 ("New PDLP and RFLP patterns produced by intron sequences indicate the presence of a previously unrecognized haplotype."); Col. 17, lines 42-44 ("Such small numbers indicate that a limited number of haplotypes are associated with the region.")	selected chromosomal region as being associated with the trait. **INTRINSIC EVIDENCE:** indication: The preamble is a limitation, and describes "[a] genomic mapping method for identifying informative, polymorphic markers and using said markers to identify a chromosomal region associated with a trait." Col. 37:41-43.
5. The method of claim 1		

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wherein said non-coding sequence is an **intron** sequence. **intron** Found in claim numbers: '762 Patent: 5, 6, 7, and 16	**intron** **JOINT CONSTRUCTION:** an untranslated DNA sequence between exons	
9. A genomic mapping method for identifying a chromosomal region associated with a trait, comprising:		
(a) obtaining genomic DNA samples from a plurality of individuals with the trait from a general population, wherein said plurality of individuals with the trait is not derived from a single family;		
(b) amplifying a plurality of non-coding sequences from a series of selected chromosomal regions in each genomic DNA sample to produce a plurality of amplified DNA sequences,		
wherein each selected chromosomal region comprises a plurality of polymorphic non-coding regions, and said plurality of polymorphic non-coding regions defines a plurality of haplotypic patterns detectable by a selected technique for analyzing genetic variation;		

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(c) **analyzing said plurality of amplified DNA sequences** to identify the haplotype of each corresponding selected chromosomal region; **analyzing said plurality of amplified DNA sequences** Found in claim numbers: '762 Patent: 9	**analyzing said plurality of amplified DNA sequences** **PROPOSED CONSTRUCTION:** observing any variation in the DNA sequence using any technique **DICTIONARY/TREATISE DEFINITIONS:** **analyze** *The Random House Dictionary of the English Language*, 2nd Ed. Unabridged, 1987 ("...determine the ... essential features of."); *The Hammond Barnhart Dictionary of Science*, by Barnhart Books, 1986 ("To determine the nature or amount of the components of (a substance)."); *Webster's Ninth New Collegiate Dictionary*, by Merriam-Webster, 1987. ("To study or determine the nature and relationship of the parts of by analysis."); *The Random House Dictionary of the English Language*, Second Edition, Random House, Inc., 1987. ("determine the elements or essential features of."); *Webster's II, New Collegiate Dictionary*, by Houghton Mifflin Company, 1995. ("To separate into elemental parts or basic principles so as to determine the nature of the whole."); Encyclopedia of Molecular Biology and Molecular Medicine (1996), pg. 57 ("There are three basic approaches for analyzing PCR-amplified products. These are dot-blot assays using allele-specific oligonucleotide (ASO) probes to detect sequence specific alleles, sequencing assays to determine the array of nucleotides contained within a particular DNA fragment,	**analyzing said plurality of amplified DNA sequences** **PROPOSED CONSTRUCTION:** applying the selected technique to said plurality of amplified DNA sequences **DICTIONARY/TREATISE DEFINITIONS:** analyzing: Webster's Ninth New Collegiate Dictionary (1989), p. 82-83. ("analyze *vt* 1: to study or determine the nature and relationship of the parts of by analysis" "analysis *n* 2a: an examination of a complex, its elements, and their relations."). **INTRINSIC EVIDENCE:** Patentee argued that "the specification describes the amplification procedure (page 42, line 21 - page 47, line 36) and the analysis of the amplified DNA using primer defined length polymorphism and RFLP analysis (page 48, lines 1-21). Thus the specification fully describes how to perform the method of Claim 1." Amendment ('856), December 21, 1993, p.13. "Because Applicant's general description of the claimed methods is as broad as the claims, Applicant submits that the specification fully describes the claimed methods." Id. at 16. "The patterns can be produced by gel electrophoresis length differences in the amplified DNA sequences or can be RFLP fragment patterns produced by digestion of the amplified DNA sequences with

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	and separation by agarose or polyacrylamide gel electrophoresis to detect differences in the size of the PCR product.") **INTRINSIC EVIDENCE:** P. 9 of the A & R dated 21-Dec-1993 of the Parent Application No.: 07/971,856 ("a genetic variation can be identified by a variety of techniques that detect such differences in sequences between different individuals... [Method comprises] identifying a genetic variation by any of the available techniques."); Col. 1, lines 34-36 ("Currently the most common method of identifying polymorphic markers is by restriction enzyme analysis using numerous restriction endonucleases."); Col. 10: 63 to Col. 11: 1 ("The prior art describes numerous instances where polymorphic loci are used to study the frequency of cosegregation of other linked polymorphic loci or genes in human pedigrees as described in the background section. In every instance where polymorphisms were used, analysis of non-coding sequence variation of this invention can be applied"); Col. 16, lines 7-14 ("Once an amplified DNA sequence containing intron sequences is produced, the primers are used to produce the corresponding amplified DNA sequences from a number of individuals. The sizes of the sequences and the fragment patterns using several restriction endonucleases can be examined to select an analytical method that demonstrates allelic and sub-allelic	one or more endonucleases." Col. 7:24-27. "To effect allele-specific or haplotype-specific amplification, at least one primer in each nested primer pair is selected so that the primer hybridizes to the DNA sequence only when the selected sequence polymorphism is present. In this way, the presence of an amplified DNA sequence indicates that the sequence polymorphism is present in the sample. This is in contrast to most prior art DNA amplification methods wherein primers bind to a conserved region and the resultant amplified DNA sequence is analyzed, usually by use of oligoprobes, for the presence of the polymorphism in the amplified sequence." Col. 26:34-44.

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	genetic diversity associated with the locus"); Col. 17, lines 29-35 ("A detailed description of selection of primers, amplification methods, and analysis of DNA sequences is provided below. Those techniques can be used initially to determine the patterns produced by common alleles/haplotypes associated with the locus. Once the common patterns are established, the patterns can be refined so that additional haplotypes associated with a locus can be distinguished."); Col. 17, lines 49-57 ("There are three major types of genetic variations that can be detected within an amplified DNA sequence and used to identify allelic and sub-allelic groups. Those variations, in order of ease of detection, are (1) a change in the length of the sequence, (2) a change in the presence or location of at least one restriction site and (3) the substitution of one or a few nucleotides that does not result in a change in a restriction site. Other variations within the amplified DNA sequence are also detectable"); Col. 17, line 64 to Col. 18, line 20, ("There are four types of techniques which can be used to detect the variations. The first is sequencing the amplified DNA sequence... The second analytical method uses allele-specific oligonucleotides or sequence-specific oligonucleotides probes (ASO or SSO probes)... A third type of analytical method detects sequences of different lengths ... and/or different numbers of sequences... A fourth and most preferred type of analytical method is based on allele/haplotype-specific	

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	amplification to detect the presence of the selected allele/haplotype."); Col. 25, lines 11-20, ("...the method used to analyze the amplified DNA sequence to characterize the allele(s) present in the sample DNA depends on the genetic variation in the sequence. When distinctions between alleles include primer-defined length polymorphisms, the amplified sequences are separated based on length... When the analysis is based on RFLP fragment patterns, the amplified sequences are digested with one or more restriction endonucleases to produce a digest and the resultant fragments are separated based on length...");Col. 25, lines 11-14 ("As discussed previously, the method used to analyze the amplified DNA sequence to characterize the allele(s) present in the sample DNA depends on the genetic variation in the sequence"); Col. 21, lines 7-14 ("For the method described herein, it is contemplated that use of more than one amplified DNA sequence and/or use of more than one analytical method per amplified DNA sequence may be required for highly polymorphic loci, loci where alleles differ by single nucleotide substitutions that are not unique to the allele, or when information regarding remote locus alleles (haplotypes) is desired")	
(d) determining the degree of restriction in haplotype heterogeneity at each selected chromosomal region for said plurality of individuals with the trait		

Claim Language (Construed Terms in Bold)	Joint Construction or	
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(e) comparing the degree of haplotype heterogeneity restriction across said selected chromosomal regions to identify a subseries of adjacent selected chromosomal regions having a greater degree of haplotype heterogeneity restriction at a central selected chromosomal region in said subseries than at selected chromosomal regions at the ends of said subseries as an indication that said central selected chromosomal region is associated with the trait.		
10. The method of claim 9		
wherein the trait is a **monogenic disease.** **monogenic disease** Found in claim numbers: '762 Patent: 10	**monogenic disease** **JOINT CONSTRUCTION:** a disease caused by a single gene	
11. The method of claim 9		
wherein the trait is a **multigenic disease.** **multigenic disease** Found in claim numbers: '762 Patent: 11	**multigenic disease** **JOINT CONSTRUCTION:** disease that is associated with more than one gene	